Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 2017;377:1119-31. DOI: 10.1056/NEJMoa1707914

 MURRAY & POOLE EXHIBIT 1039

Supplement

Ridker et al, Anti-Inflammatory Therapy with Canakinumab for Atherosclerotic Disease

This supplement contains the following items:

1. **Summary of the amendments to the protocol**
2. **The original protocol and final protocol with amendments**
3. **Summary of the amendments to the statistical analysis plan**
4. **The original statistical analysis plan and final statistical analysis plan**

Amendment 9

Amendment Rationale

CACZ885M2301 Protocol Amendment 9 provides details for the study extension described in the current protocol. Following accrual of the target number of primary events, eligible patients will have the option to continue study participation in the extension phase at their end of study visit. The objective of the extension phase is to obtain further follow-up information on long-term safety on continued exposure to canakinumab in trial participants. Additionally, as defined in the current protocol, the study drug washout in the cohort of prediabetic patients who did not progress to diabetes during the pivotal phase will assess the durability of any potential antidiabetic effect of canakinumab after discontinuation of therapy. Persistence of a potential effect of canakinumab on quality of life and the impact of a treatment switch to the open-label dose on quality of life will also be explored. Patients who choose to participate will remain on their pivotal phase blinded assigned treatment arm for the first three extension phase visits, except for prediabetic patients who will undergo a 6-month study drug washout by skipping two doses of their pivotal phase blinded assigned treatment arm. After the database from the pivotal study is locked all participants will be switched to an open-label dose of 150 mg canakinumab. The 150 mg dose is predicted to have the highest likelihood of having the most favorable benefit: risk ratio based on biomarker and clinical data from phase II studies in Type 2 diabetics. The final canakinumab dose will be based on the results from the pivotal phase. The transition to an intermediate dose of 150 mg will avoid further placebo treatment until the final dose of canakinumab is implemented at the study sites. The extension phase will continue in an individual country for a minimum of two years from the date of the first patients enrolled in that country. The maximum duration of the extension phase will be 2.5 years from the date of the first patient enrolled in that country or until marketed product is available in that country, whichever comes first. While the extension phase is then deemed complete the safety follow-up is anticipated to be continued in registries following study results and discussion with Health Authorities.

Changes to the protocol

The described changes under the amendment rationale are implemented throughout the protocol.

In addition, the following updates, clarifications and omissions are included in this protocol amendment:

- Implementation of global and local registries post approval will be subject to discussion and agreement with health authorities during Biologic License Application (BLA)/Marketing Authorization Application (MAA) review and will be conducted via separate protocols. Section 5.5.10 updated to reflect this.

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- Section 7.1: described the reporting of adverse events during the extension phase. During the extension phase, endpoints will no longer be collected. Hence, the study specific exemption granted from the Health Authorities not to report study endpoints as serious adverse events/adverse events in the pivotal phase does not apply to the extension phase. During the extension phase ALL adverse events will be reported as AEs following the procedures described in Section 7.1 and Section 7.2.
- Section 7.2: clarification regarding the instructions for Serious Adverse Event (SAE) reporting, allowing also electronic SAE reporting
- Section 7.3 added to describe reporting of study treatment errors including misuse/abuse during the extension phase of the study
- Section 7.6.2 added that the Infections Adjudication Committee will not adjudicate cases during the extension phase
- Section 7.6.3 added that the Malignancy Adjudication Committee will not adjudicate cases during the extension phase
- Section 10.5 added to describe the Quality Management system that applies to this trial.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~strike through red font for deletions~~ and red underlined for insertions. A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, sites are required to submit for approval an updated informed consent that covers the extension phase of the study, which will be signed by patients before they move into main drug dispensing period (Visit 201 and beyond) of the extension phase.

Other minor updates and corrections were also included.

Summary of previous amendments

Amendment 8

Amendment Rationale

CACZ885M2301 Protocol Amendment 8 adjusts the number of patients to be randomized into the study from 17,200 patients to approximately 10,000 patients. This change is not based on safety or efficacy concerns, instead it resulted from a strategic decision that considered the higher than anticipated primary event endpoint rate observed thus far.

Importantly, the study objectives and power remain unchanged and the study will still complete when 1,400 primary event endpoints are accrued as originally planned. The elapsed calendar time to reach the conclusion of the study is now estimated to be approximately 6 years (instead of 5 years) of treatment and follow-up from the start of enrollment in the trial to when 1,400 primary cardiovascular events have been accrued.

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Protocol Amendment 8 also introduces the option to perform a futility analysis earlier than the first planned efficacy interim analysis (IA) (at approximately 50% primary events) but only after a sufficient number of primary events are accrued, i.e., >25%. This may be performed by the DMC in consideration of the longer period of time that may be needed to reach the first IA from the start of enrollment.

Changes to the protocol

The described changes in the amendment rationale are implemented throughout the protocol.

The following minor updates, clarifications and omissions are included in this protocol amendment:

- In accordance with the change in sample size, the total planned patients screened changed from 29,000 to 17,000.
- Spelled out the CANTOS acronym (Section 3.1)
- Informed that CACZ885M2301 Sub-study S1 and S2 have been terminated. Of note, the Sponsor decision to terminate these sub-studies was not due to safety or efficacy concerns (Section 3.1).
- Clarified that the full committee DMC safety reviews will occur on a six-month basis and the DMC chair will review the safety data on a three-month basis (Section 3.5).
- In Section 5.5.8, added information specifying that the patient contact information should be reviewed at each visit and clarified the process for visits/patient contact following study drug discontinuation.
- Added Years 5 and 6 to Table 6-1
- In Section 6.5.7, informed as a correction that Allergies/Immunological are not adjudicated events.
- Corrected the following statement noting that all malignancies including basal cell carcinoma should be reported as SAEs meeting the criteria of "medically significant" (Section 7.1)
- In the site monitoring section (Section 8.1), incorporated the various methods utilized to ensure protocol and GCP compliance and the quality/integrity of the sites' data. Continuous remote monitoring and a central analytics organization have been added as a complement to field monitoring.
- A discussion of the currently observed event rates, the impact on trial duration and the lack of an impact on study power was added to the statistical section.

Other minor updates and corrections were also included.

Amendment 7

Short summary of the amendment rationale and major changes

In order to comply with a Health Authority (PMDA) request from Japan, Visit 1 screening tests for HBc antibody and HBs antibody are added in Japan only to prevent enrolling Japanese patients who have a history of hepatitis B infection and/or are hepatitis B carriers. In

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order to comply with the Central Ethics Committee request in Croatia, specific language regarding post-menopausal status determination in women less than 50 years of age is added for Croatia only.

Additional updates and clarifications were also noted in this protocol amendment such as allowing the prescreen hsCRP if performed at the central laboratory less than 60 days prior to Visit 2 and ≥ 2mg/L to be used as the qualifying hsCRP, clarifying the tuberculosis status determination for study entry, informing that recruitment will target approximately 50% of randomized patients with an index MI 30 days to 12 months prior to randomization and 50% with an index MI >12 months prior to randomization, and noting that for patients whose treatment is stopped as a result of a data monitoring committee recommendation to suspend treatment in one dose group, follow-up for cardiovascular and safety events will continue at 6 month intervals. The amendment also removed mention of a recruitment duration of 21 months and informed that the elapsed calendar to time to reach the conclusion of the study is estimated to be approximately 5 years of treatment from the start of enrollment to the occurrence of when 1,400 patients have had confirmed adjudicated primary cardiovascular events. In Section 5.5.8, additional clarity was added to the situations under which patients may restart study treatment, the liver function test discontinuation criteria was aligned with recent company guidance for liver enzyme elevations, and it was noted that patients who develop any malignancy other than excised basal cell skin carcinoma must discontinue from study treatment. Lastly, the Immunogenicity methodology was updated, the total vascular events composite was corrected to include coronary angiogram, and the amendment informed of two separate adjudication committees (Infection and Malignancy) to replace the previously described Allergy, Infection and Malignancy Adjudication committee.

Other minor updates and corrections were also included.

Amendment 6

Short summary of the amendment rationale and major changes

Following Health Authority feedback on the doses, Amendment 6 included a lower 50 mg dose arm in order to examine canakinumab's dose response in preventing recurrent cardiovascular events, and to determine if a dose lower than 150 mg would have a favorable risk benefit ratio. This was in agreement with Health Authority feedback concerning the potential inability to adequately examine canakinumab's dose response in preventing recurrent cardiovascular events when studying the 150 and 300 mg dose only, which may not result in adequate separation of efficacy measurements and lack of data on doses less than 150 mg quarterly, which may have a favorable safety profile.

Amendment 6 also increased the sample size to 17,200 patients in order to have the power of having at least one dose significant of ≥ 90% and to also have ≥ 80% power for the 50 and 150 mg doses individually when assuming that all doses have a 20% relative risk reduction. Following this amendment, randomized allocation to the four trial arms will be unbalanced in order to optimize power, now that three active arms are compared versus a common control arm. Overall across both trial parts an approximately 1.5:1:1:1 (placebo: 50 mg canakinumab: 150 mg canakinumab: 300 mg canakinumab) allocation is targeted.

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Amendment 6 also clarified the documentation requirements for spontaneous MI inclusion criteria, women of child-bearing potential exclusion criteria and tuberculosis exclusion criteria. This amendment included an age-related macular degeneration case report form to collect data on exploratory hypothesis that canakinumab may impact incidence of age-related macular degeneration and additionally specified that blood for biomarkers would be collected on an annual basis at selected sites. The analysis plan was updated to insert the evaluation of the 50 mg dose into the pre-specified closed testing procedure for primary and key secondary endpoints.

Amendment 5

Short summary of the amendment rationale and major changes

In order to comply with the European Competent Authorities request in the context of the Voluntary Harmonization Procedure (VHP), additional information regarding potential early study termination was added to Section 5.5.1.

Amendment 4

Short summary of the amendment rationale and major changes

In order to comply with a Health Authority (PMDA) request from Japan, additional instruction for reporting of specific pre-defined endpoints in Japan was added. This instruction applies to Japan only. Section 7.2 describes the specific pre-defined endpoints in Japan that require expedited reporting to Novartis Pharma K.K.

Amendment 3

Short summary of the amendment rationale and major changes

In amendment 1 an early high dose regimen was selected for both the 150 mg and 300 mg arms whereby each of these doses would be administered twice, over two week period, at randomization (month 0) and at week 2 (month 0.5). To provide a greater separation between the active-dose arms, the early high dose regimen in the 150 mg arm has been removed. This is in agreement with health authority feedback.

An exploratory objective has been added to examine the impact of the early high dose regimen between 300 mg arm (with the early high dose administered) and the 150 mg arm (with no early high dose administered) on clinical cardiovascular events.

To maintain the integrity of the study the data from the interim analyses of T2DM related glycemic control parameters will not be shared with Novartis management as noted in Section 3.5. This is compliant with health authority feedback.

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Amendment 2

Short summary of the amendment rationale and major changes

In the original protocol all deaths, cardiovascular and non-cardiovascular, were reported as potential endpoints and were adjudicated by cardiovascular clinical adjudication committee. Only those deaths, which the adjudication committee determined to be non-cardiovascular deaths, were reported as SAEs after adjudication was completed.

In order to comply with the recent 21 CFR Parts 312 and 320 regulation and draft FDA guidance on Safety Reporting Requirements for INDs and BE/BA Studies, section on reporting clinical endpoints (21 CFR 312.32 (c)(5)), protocol section 7.2 has been revised to assure that certain selective study drug related non-cardiovascular deaths will be reported both as study endpoints and SAEs as soon as study site has been notified of such events without waiting for adjudication committee to complete the adjudication process. This revised SAE reporting procedure fulfills requirements in the above mentioned regulation and draft FDA guidance.

In addition, the definition of pre-diabetes was revised to include impaired fasting glucose, FPG 100-125 mg/dL (5.6-6.9 mmol/L), as a criterion together with the original criterion of HbA1c 5.7-6.4% based on FDA feedback on IND filing of this protocol.

Amendment 1

Short summary of the amendment rationale and major changes

In the original protocol, the dose of canakinumab that provided near maximal biomarker suppression was selected as 150 mg quarterly, and an additional lower dose was selected below this level at 50 mg quarterly. However, as more efficacy data has been analyzed and safety data has accumulated for canakinumab in rheumatoid arthritis and gout patients, safety across a wide range of doses has continued to show a well tolerated and safe profile following higher dose administration. Thus the opportunity has arisen for the CACZ885M2301 protocol to evaluate a higher canakinumab dose since the dose needed for adequate IL-1β neutralization within the plaque or systemically in inflammation-based atherosclerosis is not established. Therefore, a higher dose might deliver greater efficacy than originally selected doses. Thus, as indicated here prior to randomization of any trial participants, the doses to be evaluated in CACZ885M2301 will be placebo s.c. quarterly, 150 mg canakinumab s.c. quarterly and 300 mg canakinumab s.c. quarterly. In addition, currently available safety data provides the opportunity to introduce an early higher dose administration in order to achieve early anti-inflammatory benefit in this high risk cardiovascular population. This induction period provides drug administration twice over a 2 week period and seeks to achieve optimal IL-1β suppression early to provide optimal clinical benefit. Thus, the CACZ885M2301 trial regimens will consist of:

(a) placebo s.c. at randomization (month 0), placebo s.c. at week 2 (month 0.5), placebo s.c. at week 12 (month 3), and then placebo s.c. quarterly;

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(b) canakinumab 150 mg s.c. at randomization (month 0), canakinumab 150 mg s.c. at week 2 (month 0.5), canakinumab 150 mg s.c. at week 12 (month 3), and then canakinumab 150 mg s.c. quarterly; and

(c) canakinumab 300 mg s.c. at randomization (month 0), canakinumab 300 mg s.c. at week 2 (month 0.5), canakinumab 300 mg s.c. at week 12 (month 3), and then canakinumab 300 mg s.c. quarterly.

Advantages of a 300 mg quarterly dose rather than the 50 mg quarterly dose and an additional early dose of canakinumab (either 150 mg or 300 mg) are supported by data that de-couples the biomarker dose effect from gene expression dose effect. The proposed dose regimens are aimed to provide optimal suppression of potential auto-induction of IL-1β and greater early suppression of IL-1β related gene expression. IL-1β auto-induction has been shown in human mononuclear blood, vascular endothelial and vascular smooth muscle cells in vitro and in rabbits in vivo where IL-1 has been shown to induce its own gene expression and circulating IL-1β level (Dinarello et al. 1987, Warner et al. 1987a, and Warner et al. 1987b). These studies suggested that IL-1 induced IL-1 gene expression may provide a positive feedback mechanism in the pathogenesis of atherosclerosis and promote atherosclerosis. This consequently suggests that suppression this feedback mechanism may provide benefits in the atherosclerotic lesion. To accommodate this change in administration of canakinumab, a week 2 visit for drug administration and safety assessments was added to the study visit schedule. The change in dosing regimen necessitated an update to the definition of the safety set. The safety set definition was based on the new Novartis Cardiovascular Clinical Science Unit standards. Similarly, the definition of the censoring date was aligned with these standards. This definition reflects that if there was contact with a patient without the patient attending a visit, then the visit date – in the absence of other information – should be the date of the last contact with the patient.

In addition, the following errors and omissions in the original protocol were corrected:

- Pharmacogenomics information was added to the protocol and study visit schedule
- Troponin I and creatinine kinase MB fraction were added for patients with elevated total creatinine kinase
- Genetics sample storage will be at the Central Laboratory
- SAE reporting instructions were corrected to direct investigators to follow instructions provided in the investigator folder
- Supraventricular tachycardia and atrial fibrillation definitions were added to the protocol
- CABG-MI definition was updated to follow universal MI definition (Thygesen et al 2007)
- Diabetes related definitions used in stratification section were updated
- PK/PD/IG sampling time-points were updated
- HOMA calculation was removed
- A confirmation of elevated ALT/AST and total bilirubin is no longer required at screening

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NOVARTIS

Clinical Development

ACZ885M/Canakinumab

Clinical Trial Protocol CACZ885M2301

A randomized, double-blind, placebo-controlled, event-driven trial of quarterly subcutaneous canakinumab in the prevention of recurrent cardiovascular events among stable post-myocardial infarction patients with elevated hsCRP

Authors:	Thuren,Tom, MacKenzie,Michele, Holzhauer,Björn, Ridker, Paul; Glynn, Robert

Document type:	Clinical Trial Protocol
EUDRACT number:	2010-022970-14
Version number:	v00 (original protocol)
Development phase:	III
Release date:	21-Sep-2010

Template Version 26-May-2009

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List of abbreviations

ADL	Activities of Daily Living
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	Body Mass Index
CABG	Coronary Artery Bypass Graph
CAPS	Cryopyrin-Associated Periodic Syndromes
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
CRF	Case Report/Record Form
CPO	Country Pharma Organization
CRO	Contract Research Organization
CV	Cardiovascular
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EOS	End of Study
FAS	Full Analysis Set
FPG	Fasting Plasma Glucose
GWA	Genome-wide association
HbA1c	Glycosylated hemoglobin
HIV	Human Immunodeficiency Virus
hsCRP	High Sensitivity C-Reactive Protein
IA	Interim Analysis
IB	Investigators Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IG	Immunogenicity

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IL-1β	Interleukin 1 Beta
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IVRS/ IWRS	Interactive Voice Response System / Interactive Web Response System
LDL	Low density lipoprotein
LFT	Liver Function Test
MACE	Major CV Disease Events
MFSI-SF	Multi Dimensional Fatigue Symptom Inventory-Short Form
MI	Myocardial Infarction
MRS	Modified Rankin Scale
NOD	New Onset Diabetes
NYHA	New York Heart Association
PCI	Percutaneous coronary intervention
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per Protocol Set
PPD	Purified protein derivative
PRO	Patient Reported Outcomes
PTCA	Percutaneous transluminal coronary angioplasty
PVD	Peripheral Vascular Disease
QFT-g	QuantiFERON-TB Gold
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SBP	Systolic Blood Pressure
Sc	Subcutaneous
SIS-16	Stroke Impact Scale
T2DM	Type 2 Diabetes Mellitus
TB	Tuberculosis
TIA	Transient Ischemia Attack

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Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	A study drug or placebo used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug.”
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IVR system
Patient number	A number assigned to each patient who enrolls in the study. When combined with the center number, a unique identifier is created for each patient in the study.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study drug	Any drug administered to the patient as part of the required study procedures; includes investigational drug and any control drugs
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

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Protocol synopsis

Title of study: A randomized, double-blind, placebo-controlled, event-driven trial of quarterly subcutaneous canakinumab in the prevention of recurrent cardiovascular events among stable post-myocardial infarction patients with elevated hsCRP

Purpose and rationale: The purpose of this trial is to test the hypothesis that canakinumab treatment of patients with MI at least one month prior to study entry and elevated hsCRP will prevent recurrent cardiovascular events. A secondary hypothesis, that canakinumab treatment in patients with MI and pre-diabetes, will prevent new onset diabetes (NOD) will also be tested. The trial is pivotal for registration for canakinumab for cardiovascular risk reduction.

Objectives:

Primary Objective

The primary objective of this clinical trial is to demonstrate the superiority of at least one dose of canakinumab compared to placebo in reducing the risk of recurrent major cardiovascular disease events (cardiovascular death, non-fatal MI and stroke) in a population of clinically stable post-MI patients with elevated hsCRP receiving standard of care.

Key and other secondary objectives

- To demonstrate superiority of canakinumab compared to placebo on the composite endpoint of CV death, non-fatal MI, stroke, and hospitalization for unstable angina requiring unplanned revascularizations.
- To demonstrate superiority of canakinumab compared to placebo on the endpoint of new onset type 2 diabetes among those with pre-diabetes at randomization
- To demonstrate superiority of canakinumab compared to placebo on the composite endpoint of all-cause mortality, non-fatal MI and stroke.
- To demonstrate superiority of canakinumab as compared to placebo on the endpoint of all-cause mortality
- To evaluate the long-term safety of canakinumab therapy in a placebo-controlled setting

Exploratory Objectives

- To explore whether canakinumab compared to placebo reduces the risk of other cardiovascular disorders with a known inflammatory component:
  - Composite of deep vein thrombosis/pulmonary embolism
  - Supraventricular tachycardia/atrial fibrillation
  - Stent thrombosis (probable or definite)
  - Hospitalization or prolongation of hospitalization due to heart failure
  - Major coronary events composite (CHD death, non-fatal MI)
  - Total vascular events composite
  - Coronary revascularization procedures (PCI or CABG)
  - Stroke by etiology
- To explore whether canakinumab compared to placebo reduces nephropathy as assessed by urinary albumin/creatinine ratio in patients with T2DM or pre-diabetes at baseline
- To explore whether canakinumab compared to placebo improves glycemic control among those with type 2 diabetes
- To explore whether canakinumab compared to placebo standard of care) affects biomarkers of cardiovascular and diabetes risk, including inflammatory biomarkers, glycemic control markers, β-cell function markers

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- To explore whether canakinumab as compared to placebo affects patient reported outcomes of tiredness, physical function and performance function and improves health status as assessed by the EQ-5D Quality of Life (QOL) assessment.
- To perform exploratory pharmacogenetic assessments to examine whether individual genetic variation in genes relating to drug metabolism, major cardiovascular events, type 2 diabetes, and the drug target pathway confer differential response to canakinumab.

Population: Participants eligible for this trial will include male and non-child-bearing potential female patients age 18 years and older who (a) have suffered a documented acute myocardial infarction at least 30 days before randomization and (b) have evidence of systemic inflammation on the basis of an hsCRP ≥ 2 mg/L despite the use of standard of care post-MI medical therapies. Standard of care post-MI background therapy includes, but is not limited to, lipid lowering, anti-hypertensive, beta blockers, and anti-platelet therapy as appropriate.

The trial will be an event-driven global trial conducted in the outpatient setting. It is anticipated that approximately 694 cardiovascular endpoints will accrue during the course of the trial (see Section 9.7 for Power Calculations). To accomplish this goal, it is expected that around 14,600 patients will need to be screened in order to randomize approximately 7,302 patients.

Key Inclusion/Exclusion criteria:

Inclusion

Patients eligible for inclusion in this study must fulfill all of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Male, or Female of non-child-bearing potential
3. Age ≥ 18 years at Visit 1.
4. Documented spontaneous MI (diagnosed according to the universal MI criteria with or without evidence of ST segment elevation) at least 30 days before randomization. (Thygesen et al 2007)
    - Diagnosis of prior MI should be based on medical history of clinical symptoms consistent with myocardial ischemia associated with elevation of cardiac biomarkers above the 99th percentile of the upper reference limit (preferably troponin) OR development of new pathological Q waves regardless of symptoms (see Appendix 3) or ECG changes associated with prior myocardial infarction (Thygesen et al 2007). For details, refer to the Universal Definition of MI (Thygesen et al 2007). Patients with MI resulting from PCI or CABG will not be eligible
5. Have an hsCRP ≥ 2 mg/L at screening (Visit 1) (which is at minimum of 28 days after qualifying MI or after any PCI performed separately from qualifying MI) on stable (at least 4 weeks) long-term medications.

Exclusion

Patients fulfilling any of the following criteria are not eligible for inclusion in this trial:

1. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/ml)
2. Women of child-bearing potential defined as all women physiologically capable of becoming pregnant, UNLESS they are
    - Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/ml (for US only: and estradiol < 20 pg/mL) or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the

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woman has been confirmed by follow up hormonal level assessment is she considered not of child bearing potential.

3. Any of the following concomitant diseases
   - Planned coronary revascularization (PCI or CABG) or any other major surgical procedure.
   - Major non-cardiac surgical or endoscopic procedure within past 6 months to Visit 1
   - Multi-vessel CABG surgery within the past 3 years
   - Symptomatic patients with Class IV heart failure (HF) (New York Heart Association [NYHA].
   - Uncontrolled hypertension (defined as an average SBP >160 mmHg or an average diastolic blood pressure (DBP) >100 mmHg at Visit 1. Patients are allowed to be re-evaluated, at the discretion of investigator for this criterion if anti-hypertensive therapy has been started or increased as a result of initial screening blood pressure above these limits. (Mancia et al 2009).
   - Uncontrolled diabetes as defined by the investigator
   - Nephrotic syndrome or eGFR < 30 mL/min/1.73 m^2 per MDRD formula or kidney transplant (regardless of renal function), Visit 1
   - Known active or recurrent hepatic disorder (including cirrhosis, hepatitis B and hepatitis C, or confirmed ALT/AST levels > 3 times ULN or total bilirubin > 2 times ULN) ,Visit 1
   - Prior malignancy other than basal cell skin carcinoma
4. A history of alcohol and/or substance abuse that could interfere with the conduct of the trial
5. History or evidence of active tuberculosis (TB) infection at Visit 1 or one of the risk factors for tuberculosis such as but not limited or exclusive to:
   - History of any of the following: residence in a congregate setting (e.g. jail or prison, homeless shelter, or chronic care facility), substance abuse (e.g. injection or non-injection) health-care workers with unprotected exposure to patients who are at high risk of TB or patients with TB disease before the identification and correct airborne precautions of the patient

   or
   - Close contact (i.e. share the same air space in a household or other enclosed environment for a prolonged period (days or weeks, not minutes or hours)) with a person with active pulmonary TB disease within the last 12 months.
6. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection, at Visit 1, determined as defined by local guidelines/ local medical practice (see also below for determination of tuberculosis status). If presence of tuberculosis is established then treatment (according to local guidelines) must have been completed prior to randomization.
7. Patients with suspected or proven immunocompromised state, including (a) those with evidence of Human Immunodeficiency Virus (HIV) infection; Patients on anti-retroviral therapy are excluded (b) those with any other medical condition which in the opinion of the investigator places the patient at unacceptable risk for participation in immunomodulatory therapy; or (c) those requiring systemic or local treatment with any immune modulating agent in doses with systemic effects e.g. high dose oral steroids. Topical, inhaled, local steroid use in doses that are not considered to cause systemic effects are permitted.
8. Live vaccinations within 3 months prior to the randomization visit or live vaccinations planned during the trial.
9. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.
10. Patients who have received an investigational drug or device within 30 days (inclusive) of Visit 1, or who are expected to participate in any other investigational drug or device study during the conduct of this trial, except for patients who have an investigational treatment

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eluting stent (DES), provided that they have completed the DES trial. FDA/country-specific drug regulatory authority approved DES devices are permitted.

11. Any biologic drugs targeting the immune system (for example, TNF blockers, anakinra, rituximab, abatacept, tocilizumab)
12. Any life threatening condition with life expectancy < 5 years, other then vascular disease that might prevent the patient from completing the study

Investigational and reference therapy:

Patients will be assigned to one of the following 3 treatment arms in a ratio of 1:1:1

- Canakinumab 150 mg quarterly subcutaneous
- Canakinumab 50 mg quarterly subcutaneous
- Placebo

For patients who are unable to tolerate the protocol-specified dosing intervals, dose interruptions are permitted in order to keep the patient on study drug. Patients are encouraged to continue study medication; however; they are allowed to interrupt and re-start medication at any time during the study at the discretion of the investigator.

Study design: The study is a Phase 3 multi-center, randomized, parallel group, placebo-controlled, double-blind event-driven global clinical trial to evaluate the benefit of quarterly subcutaneous canakinumab doses compared to placebo among stable post-MI patients receiving standard of care therapy who have been selected for an elevated inflammatory burden as determined by hsCRP $\geq$ 2 mg/L. The index qualifying MI must have occurred at least 30 days prior to randomization. Standard of care post-MI background therapy includes but is not limited to appropriate lipid lowering, anti-hypertensive, beta blockers, and anti-platelet therapy as defined by local guidelines.

Screening will take place no earlier than 28 days after the index MI and on stable (at least 4 weeks) long term medication. Evaluations will include hsCRP and determination of tuberculosis status among other measurements and procedures. After screening visit, patients may be randomized, as soon as, results from screening laboratory and other studies are available. However, this can be no earlier than 30 days after the index MI. For patients who underwent PCI at different hospital admission than the qualifying MI; screening can be initiated no earlier than 28 days following this procedure. For patients who have history of CABG; screening can be initiated no earlier than 3 years after the procedure regardless of timing of the qualifying MI.

Randomization will be stratified by time since most recent index myocardial infarction with 50% of the population in each strata (30 days to <6 months and ≥6 months). The Steering Committee and Sponsor will monitor the patient profiles during recruitment phase and may increase or restrict enrollment of certain sub-groups of patients to avoid imbalances. There will be no upper limit for post MI for inclusion into the trial. The trial is event driven and designed to complete when a total of 694 patients have experienced a primary cardiovascular endpoint. Double blind treatment will be continued until the target number of primary cardiovascular endpoints has been reached. Sites will then be notified to have all patients return to complete an EOS visit. The elapsed calendar time to reach conclusion of the study is estimated to be a total of 4.5 years of treatment and follow-up from the start of enrollment in the trial to the occurrence of 694 confirmed cardiovascular events. These estimates are based on the assumption that the time necessary to complete enrollment in the study will be approximately 18 months.

Interim analyses (IA) of efficacy, futility and safety will be carried out during the study in order to avoid exposing study patients to ineffective treatment or undue risks or to allow study discontinuation in case of overwhelming efficacy. Two interim analyses of efficacy will be performed when approximately 50% of the target number of patients with primary endpoints have been accumulated and the second one when approximately 75% of the planned number of patients with primary endpoints are available.

Following a successful completion of this trial all patients who are either normoglycemic or have T2DM will be enrolled in an open label follow-up study where participants will be treated with canakinumab in

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order to determine long term safety and efficacy of canakinumab treatment. Patients with pre-diabetes at the end of this trial (last in trial HbA1c 5.7-6.4%) will first enter into the 6 month washout phase followed by the open label follow-up study including re-starting canakinumab treatment. This safety follow-up study will collect safety events to be determined based on canakinumab profile in the main trial and major cardiovascular adverse events as defined in the primary endpoint of the main trial at bi-annual visits. An extension protocol with detailed study information including length of the follow-up will be developed for the open label follow-up study.

Efficacy assessments:

Primary efficacy assessment:

The primary endpoint is defined as the time to the first event of a major cardiovascular event (MACE) occurring during the double-blind treatment period, which is a composite of CV death, non-fatal MI, and stroke. An independent adjudication committee that is blinded to treatment assignments will review and adjudicate all clinical events that constitute the composite endpoint.

Key secondary efficacy assessments:

Key secondary efficacy assessments will comprise:

- Time to first event of a composite cardiovascular endpoint consisting of the primary endpoint, and hospitalization for unstable angina requiring unplanned revascularization
- Time to new onset type 2 diabetes among those with pre-diabetes at randomization (time to NOD)

Other secondary efficacy assessments:

Other secondary efficacy assessments will comprise

- Time to first event of, non-fatal MI, stroke and all-cause mortality composite
- Time to all-cause mortality

Exploratory efficacy assessments

Exploratory efficacy assessments are described in (Section 6.4.2) of the clinical study protocol.

Safety Assessments*:*

- Laboratory evaluations
- Height and Weight
- Adverse events and serious adverse events, including cardiovascular events, malignancies, and infections
- Discontinuation due to AEs
- Hypoglycemia events
- Injection site reactions
- Physical Examination
- Biomarkers
- Vital Signs
- ECG

Serious allergies/immunological events, serious infections, and malignancies adverse events will be monitored carefully during this trial because these adverse events represent hypothetical mechanism of action related risks of canakinumab therapy.

Other Assessments:

- Assessment of Glycemic Control for T2DM
- Stroke Functional Assessment Sub-Study

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- The Modified Rankin Scale, MFSI-SF, SIS-16, EQ-5D,SF-36 Health State Classification, Visual Analogue Scale 'Thermometer'
- Pharmacokinetics, pharmacogenetics, other biomarkers

Data analysis:

The primary statistical hypotheses are:

- H_{11}: The hazard rate of first adjudication committee confirmed MACE in the canakinumab 50 mg dose group is greater or equal to than in the placebo group
- H_{21}: The hazard rate of first adjudication committee confirmed MACE in the canakinumab 150 mg dose group is greater or equal to than in the placebo group

Each tested versus the one-sided alternative that the hazard rate is smaller for the respective active dose group than in the placebo group.

These hypotheses will be tested by comparing each dose to placebo with a log-rank test stratified by time since index MI using Peto's exact method (Peto 1972) for handling ties on the FAS according to the intent-to-treat principle. The family-wise error rate will be controlled at the two interim analyses and the final analysis using a closed testing procedure that initially assigns all the available significance level equally to the two primary null hypotheses relating to the two doses. Key secondary endpoints for a dose are only tested after the rejection of the primary null hypothesis for that dose.

A fixed Bonferroni split of the one sided alpha will be used to account for the two efficacy interim analyses and the final analysis, with a significance level of 0.01% for the first efficacy interim analysis, 0.04% for the second efficacy interim analysis and 2.45% for the final analysis. In this fashion the family-wise type I error rate will be controlled at the one-sided 2.5% level.

The hazard ratios and their associated confidence intervals will be estimated by means of a Cox proportional-hazards model stratified by time since index MI (< 6 months, ≥ 6 months) using treatment (canakinumab doses and placebo) as a factor in the model using Peto's exact method (Peto 1972) for handling ties. Kaplan-Meier plots will be presented to summarize the time to first event in the composite endpoint, by presenting the time-dependent cumulative frequency and percentage of patients who reach the primary composite endpoint by treatment group.

The components of the composite primary efficacy endpoint (CV death, fatal or non-fatal MI, fatal or stroke) will also be analyzed individually in order to evaluate their contributions to the overall treatment effect.

Based on the FAS, all key secondary efficacy variables will be analyzed with a log-rank test stratified by time since index MI and displayed by means of Kaplan-Meier plots according to treatment.

The secondary efficacy variable corresponding to new onset type 2 diabetes in patients with pre-diabetes at randomization will be the time from randomization to the first occurrence of repeated FPG ≥ 126 mg/dL or of a repeated HbA1c $\underline{\geq}$ 6.5% or of the start of new anti-diabetic medication. Due to the discrete nature of the time points when new onset of type 2 diabetes can be determined, events identified at the same visit time point for different patients will be considered as tied events and (Peto 1972) exact method for handling ties will be used.

Exploratory time-to-event outcomes will be analyzed using Cox regression models including treatment with time since index MI as a stratification variable, along with Kaplan-Meier analyses. Exploratory continuous outcome variables (i.e. change from baseline of HbA1c, biomarkers, and patient reported outcomes, etc.) will be analyzed using both a repeated measures analysis of covariance adjusted for baseline value, as well as descriptively..

Safety

The incidence of adverse events (new or worsened) will be summarized by primary system organ class (SOC), preferred term, severity and relationship to study drug. The incidence of death, SAEs, and AEs leading to discontinuation will be summarized separately by primary system organ class and preferred term. SAEs will be narrated.

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The incidence of adverse events related to cardiovascular events in constellations relevant for a description of safety and death, as well as serious infections and malignancy will be specifically investigated. Appropriate time to event assessments will be used if warranted.

Laboratory data will be summarized by shift tables and categorical analyses using extended normal ranges if thresholds of interest are identified based on baseline to most extreme post-baseline value, with summary statistics of raw and change from baseline by visits. Furthermore, notable values will be flagged in data listings.

Sample Size Calculation

With a sample size of 7,302 randomized patients recruited within 1½ years of study initiation and assigned in a 1:1:1 allocation ratio to canakinumab 150 mg, canakinumab 50 mg, and placebo it is expected that 694 patients will experience a primary endpoint within 4½ years of study initiation. 694 endpoints are necessary to achieve a power of approximately 90% to demonstrate the superiority of at least one dose of canakinumab compared to placebo on the primary endpoint assuming a relative hazard reduction of 23.9% for both active doses.

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1 Introduction

1.1 Background

Atherosclerosis is a disease characterized by chronically high inflammatory state. Arterial inflammation and endothelial dysfunction play key roles at all stages of the atherothrombotic process. Inflammatory mediators are intimately implicated with the cascade of events leading to atherosclerotic plaque initiation, progression and rupture. Vascular endothelial cells express a variety of adhesion molecules that recruit monocytes when chronically exposed to noxious stimuli or pathological conditions. Adverse conditions such as hyperlipidemia are associated with enrichment of a pro-inflammatory subset of monocytes. These monocytes apparently enter the intima under the influence of chemotactic stimuli and engulf modified low density lipoprotein (LDL) and cholesterol crystals (Duewell et al 2010). The material internalized by phagocytes induces phagolysosomal damage and subsequent leakage of contents into cytosol to activate inflammasomes and caspase 1, and consequently the generation of interleukin-1b (IL-1β) from pro-interleukin-1β.

Interleukins are key mediators in the chronic vascular inflammatory response in cardiovascular (CV) disease and have been demonstrated in animal models and in humans to be potent modulators of pro-inflammatory processes. The fact that these cytokines and their receptors are highly expressed and are functional in almost all cell types implicated in the pathogenesis of atherosclerosis including smooth muscle cells, certain subset of macrophages and T cells as well as endothelium support the role of interleukins in vascular disease. For example IL-1β is a potent smooth muscle cell mitogen, an activator of endothelial cells and increases extra cellular matrix and collagen deposition which plays a role in plaque burden and arterial thickening. Furthermore, lack of IL-1β or ablation of IL-1 receptor has been shown to decrease severity of atherosclerosis in apoE deficient mice. Thus, antagonism of the IL-1β mediated inflammation is a primary and attractive target for ameliorating the vessel wall inflammation associated with atherosclerosis.

Canakinumab (ACZ885) is a fully human monoclonal anti-human IL-1β antibody of the IgG1/k isotype, being developed for the treatment of IL-1β driven inflammatory diseases. It is designed to bind to human IL-1β and thus blocks the interaction of this cytokine with its receptors. The antagonism of the IL-1β mediated inflammation using canakinumab in lowering high sensitivity C-reactive protein (hs-CRP) and other inflammatory marker levels has shown an acute phase response in patients with Cryopyrin-Associated Periodic Syndrome (CAPS) and rheumatoid arthritis (data on file). This evidence has been replicated in patients with type 2 diabetes mellitus (T2DM) using canakinumab (data on file), and with other IL-1β antibody therapies in development.

Therefore, canakinumab is expected to reduce the risk of future occurrence of major cardiovascular events in patients with recent past myocardial infarction (MI) by preventing IL-1β mediated vascular wall inflammation and endothelial dysfunction.

Atherosclerotic vascular disease is the primary cause of morbidity and mortality in individuals with and without T2DM. The progression of atherosclerosis from endothelial dysfunction to vascular occlusion or to plaque rupture is the underlying mechanism responsible for many

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debilitating and life-threatening diseases such as MI, stroke and peripheral vascular disease (PVD). These diseases occur at higher frequency in T2DM patients and continue to increase despite use of current optimal therapies. There is also higher mortality rate after first MI in patients with T2DM compared to those without T2DM. Mortality associated with impaired glucose tolerance is 1.96 times higher compared to normal glucose tolerance. Thus novel therapies that may improve vascular function, decrease atherosclerotic burden, and translate to a decrease in cardiovascular events would fill a significant unmet medical need.

T2DM is also a disease that is characterized by a high inflammatory state. Pre-clinical data suggests IL-1β is of key importance in the progressive functional impairment and destruction of β-cells in type 2 diabetes. Pancreatic β cells secrete IL-1β in response to elevated glucose exposure promoting further impairment of cellular viability via an autocrine action. IL-1β antagonism inhibits β cell death, promotes β cell proliferation, potentiates β cell glucose-induced insulin secretion and improves insulin sensitivity. Blocking IL-1β activity with an IL-1 receptor antagonist as well as a neutralizing IL-1β antibody in clinical trials reduced HbA1c. Neutralization of IL-1β activity in the pancreatic islets is thus emerging as an attractive target for the treatment and prevention of type 2 diabetes. For T2DM prevention canakinumab's primary direct action is expected to prevent the IL-1β mediated destruction of pancreatic β-cells and thus prevent or delay progression of disease, which to date is a completely unmet need.

Therefore, canakinumab is expected to prevent new onset T2DM in patients with a recent past MI and that are pre-diabetic, and who are at risk of developing T2DM.

As demonstrated in a comprehensive 2010 meta-analysis of 54 prospective cohort studies, the inflammatory biomarker hsCRP is an independent risk factor for future cardiovascular events that (a) has a magnitude of effect similar to or larger than that of blood pressure or cholesterol and (b) has long-term stability and reproducibility at least as good as these widely-accepted risk factors (Kaptoge et al 2010). Abundant clinical trial data further demonstrate that persistent elevations of hsCRP are a major risk factor of recurrent vascular risk following myocardial infarction; for example, as demonstrated in the PROVE IT-TIMI 22 (Ridker et al 2005) and A-to-Z (Morrow et al 2006) trials. In both trials patients with known vascular disease and persistent elevation of hsCRP were at roughly double the risk for recurrent events compared to those with normal hsCRP levels. Further, stratification by hsCRP has proven highly effective in determining populations in whom added cardiovascular benefits are observed with the use of efficacious lipid lowering agents which also possess, anti-inflammatory properties. This has been proven in primary prevention studies as including the AFCAPS/TexCAPS (Ridker et al 2001) and JUPITER trials (Ridker et al 2008, Ridker et al 2009) as well as in the setting of congestive heart failure (CHF) in the CORONA trial where efficacy of intervention was seen only among those with hsCRP > 2 mg/L. Indeed, in this latter example, had stratification been done by hsCRP on an a priori basis, the trial would have been reported out as an overwhelming positive rather than as a null finding (McMurray et al 2009)

A direct anti-inflammatory agent could, in theory, be tested at any stage of the atherothrombotic process. However, the most appropriate population to test this hypothesis is one in which (a) patients are known to be at increased risk despite current therapy, and (b) there is biochemical evidence of a persistent heightened inflammatory response despite usual

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care. Recognizing these constraints, a primary prevention population would be infeasible due to the exceptionally large sample size required and because an extremely low side effect profile is typically required in that setting. In contrast, patients who have survived a MI, are clinically stable, and who have persistently elevated hsCRP levels despite aggressive treatment are an optimal population in which to undertake a test of the inflammatory hypothesis of atherothrombosis. This population is no longer at risk for plaque rupture due to altered wound healing, yet remains at high risk for recurrent vascular events despite use of all accepted therapies. If alternatively designed to enroll post-MI patients without regard to hsCRP, the proposed trial would substantially lose power and would expose large numbers of individuals with already controlled inflammation to IL-1β inhibition. All of these effects would result in an adverse shift in the benefit to risk ratio as well as greatly increase study costs.

1.2 Purpose

The purpose of this trial is to test the hypothesis that canakinumab treatment of patients with MI at least one month prior to study entry and elevated hsCRP will prevent recurrent cardiovascular events. A secondary hypothesis, that canakinumab treatment in patients with MI and pre-diabetes, will prevent new onset diabetes (NOD) will also be tested. The trial is pivotal for registration for canakinumab for cardiovascular risk reduction.

2 Study objectives

2.1 Primary objective

The primary objective of this clinical trial is to demonstrate the superiority of at least one dose of canakinumab compared to placebo in reducing the risk of recurrent major cardiovascular disease events (cardiovascular death, non-fatal MI and stroke) in a population of clinically stable post-MI patients with elevated hsCRP receiving standard of care.

2.2 Secondary objectives

Key secondary efficacy objectives

- To demonstrate superiority of canakinumab compared to placebo on the composite endpoint of CV death, non-fatal MI, stroke, and hospitalization for unstable angina requiring unplanned revascularizations.
- To demonstrate superiority of canakinumab compared to placebo on the endpoint of new onset type 2 diabetes among those with pre-diabetes at randomization

Other secondary efficacy objectives

- To demonstrate superiority of canakinumab compared to placebo on the composite endpoint of all-cause mortality, non-fatal MI and stroke.
- To demonstrate superiority of canakinumab as compared to placebo on the endpoint of all-cause mortality

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Safety objective

- To evaluate the long-term safety of canakinumab therapy in a placebo(standard of care) - controlled setting

2.3 Exploratory objectives

- To explore whether canakinumab compared to placebo reduces the risk of other cardiovascular disorders with a known inflammatory component:
    - Composite of deep vein thrombosis/pulmonary embolism
    - Supraventricular tachycardia/atrial fibrillation
    - Stent thrombosis (probable or definite)
    - Hospitalization or prolongation of hospitalization for heart failure
    - Cardiovascular death, non-fatal MI, stroke and all-cause mortality composite
    - Major coronary events composite (CHD death, non-fatal MI)
    - Total vascular events composite
    - Coronary revascularization procedures (PCI or coronary artery bypass graph (CABG))
    - Stroke by etiology
- To explore whether canakinumab compared to placebo reduces nephropathy as assessed by albumin/creatinine ratio in patients with T2DM or pre-diabetes at randomization
- To explore whether canakinumab compared to placebo improves glycemic control among those with type 2 diabetes
- To explore whether canakinumab compared to placebo affects biomarkers of cardiovascular and diabetes risk, including inflammatory biomarkers, glycemic control markers, β-cell function markers
- To explore whether canakinumab as compared to placebo affects patient reported outcomes of tiredness, physical function and performance function and improves health status as assessed by the EQ-5D Quality of Life (QOL) assessment.
- To perform exploratory pharmacogenetic assessments to examine whether individual genetic variation in genes relating to drug metabolism, major cardiovascular events, type 2 diabetes, and the drug target pathway confer differential response to canakinumab.

3 Investigational plan

3.1 Study design

The study is a Phase 3 multi-center, randomized, parallel group, placebo-controlled, double-blind event-driven global clinical trial to evaluate the benefit of quarterly subcutaneous canakinumab doses compared to placebo among stable post-MI patients receiving standard of care therapy who have been selected by an elevated inflammatory burden as determined by hsCRP > 2 mg/L. The index qualifying MI must have occurred at least 30 days prior to randomization. There is no upper limit for post MI for inclusion into the study. Standard of

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care post-MI background therapy includes but is not limited to appropriate lipid lowering, anti-hypertensive, beta blockers, and anti-platelet therapy as defined by local guidelines. Patients should also be instructed to follow heart healthy (low fat) diet and regular exercise program.

Pre-Screening: Pre-screening is a key element to successfully identifying the correct patients to be screened for this clinical study. All patients should have an available hsCRP value prior to the time of screening. The available hsCRP value should be at least 28 days after a cardiovascular event or procedure or major surgical procedure, and must be less than 60 calendar days prior to screening. The Pre-screening visit should be used after review of the patients charts to determine patients eligibility and to obtain an hsCRP value, which is to be run locally, for those potentially eligible patients who do not have one available.

Screening: Screening will take place no earlier than:

- 28 days after the index MI and on stable long term medication.
- 28 days after a PCI if it was during a different hospital admission than the qualifying MI. Screening can only be initiated following this procedure.
- 3 years post a CABG procedure regardless of timing of the qualifying MI.

All screened patients must be called into the IVRS. Screening evaluations will include hsCRP and determination of tuberculosis status among other measurements and procedures. After screening visit, patients may be randomized, as soon as, results from screening laboratory and other studies are available. However, this can be no earlier than 30 days after the index MI.

The time between screening and randomization should be approximately 4 weeks. Patients may be randomized as soon as eligibility assessments have been completed. Generally rescreening is not allowed. However, patients may be re-evaluated as noted in the inclusion and exclusion Sections (only applicable for out of range systolic and diastolic blood pressure). Patients re-evaluated will retain their screening number and be randomized or screen failed based upon the result of the re-evaluation.

Randomization will be stratified by time since most recent index myocardial infarction with 50% of the population in each strata (30 days to <6 months and ≥6 months). Patients should be hemodynamically stable at the time of randomization. The Steering Committee and Sponsor will monitor the patient profiles during recruitment phase and may increase or restrict enrollment of certain sub-groups of patients to avoid imbalances. There will be no upper limit for post MI for inclusion into the trial. Once randomized, patients will return to the clinic for scheduled visits as shown in the study assessment schedule. Some assessments at these visits will include physical examinations, vital sign measurements, electrocardiogram (ECG) , instruction on how to follow a heart healthy (low fat) diet and regular exercise program and clinical laboratory measurements including glucose control, lipids, biomarkers, and routine safety assessments..

Patients will have scheduled assessments at 6 weeks after randomization and quarterly visits thereafter to evaluate safety and the occurrence of any trial endpoints, as well as, to receive quarterly subcutaneous injections of active therapy and/ or placebo. Genetic blood samples and biomarker samples collected at randomization, month 3, one year and end of study (EOS) visit will be shipped to the Data and Laboratory Coordinating Center for long term storage.

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Upon completion of the study these samples will be analyzed for cardiovascular and metabolic biomarkers and genetic analysis, if prior written informed consent is obtained.

The trial is event driven and designed to complete when a total of 694 patients have experienced a primary cardiovascular endpoint. Double blind treatment will be continued until the target number of primary cardiovascular endpoints has been reached. Sites will then be notified to have all patients return to complete an EOS visit. The elapsed calendar time to reach conclusion of the study is estimated to be a total of 4.5 years of treatment and follow-up from the start of enrollment in the trial to the occurrence of 694 confirmed cardiovascular events. These estimates are based on the assumption that the time necessary to complete enrollment in the study will be approximately 18 months.

Following a successful completion of this trial all patients who are either normoglycemic or have T2DM will be enrolled in an open label follow-up study where participants will be treated with canakinumab in order to determine long term safety and efficacy of canakinumab treatment. Patients with pre-diabetes at the end of this trial (based on the last available HbA1c 5.7-6.4%) will first enter into the 6 month washout phase followed by the open label follow-up study including re-starting canakinumab treatment. This safety follow-up study will collect safety events to be determined based on canakinumab profile in the main trial and major cardiovascular adverse events (AE) as defined in the primary endpoint of the main trial at bi-annual visits. An extension protocol with detailed study information including length of the follow-up will be developed for the open label follow-up study.

Patients who discontinue study treatment

Every attempt to determine follow-up status of patients who discontinue study treatment, for a*ny* reason prior to the completion of the trial, must be made unless prohibited by local regulations. It is required that these patients are contacted at least 3 months post last dose of medication; and then as per study schedule to ensure all endpoints (safety and efficacy) are collected and reported. It will be at the discretion of the site staff to determine if these patients will be contacted by phone or attend the regularly scheduled visits.

Any patient who stops study treatment, withdrawals consent (if re-consented) or becomes no longer lost to follow up, is allowed to re-start the study treatment at the discretion of the investigator regardless of length of time off study treatment.

End of Study Follow-up for all pre-diabetic patients

Once all study endpoints have been reached and the site staff is contacted to have all patients return for their EOS visit, any patient with a pre-diabetic status (based on the last available laboratory results) will enter into an additional 6 month follow-up period without study treatment. At the end of this follow-up period, new onset diabetes endpoint measurement using HbA1c will be repeated. Maintenance (or increase) in the placebo subtracted HbA1c and FPG difference between canakinumab and placebo treated patients will imply that improved glucose control in-trial was not the reason for prevention of new onset diabetes mellitus.

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Sub-Studies

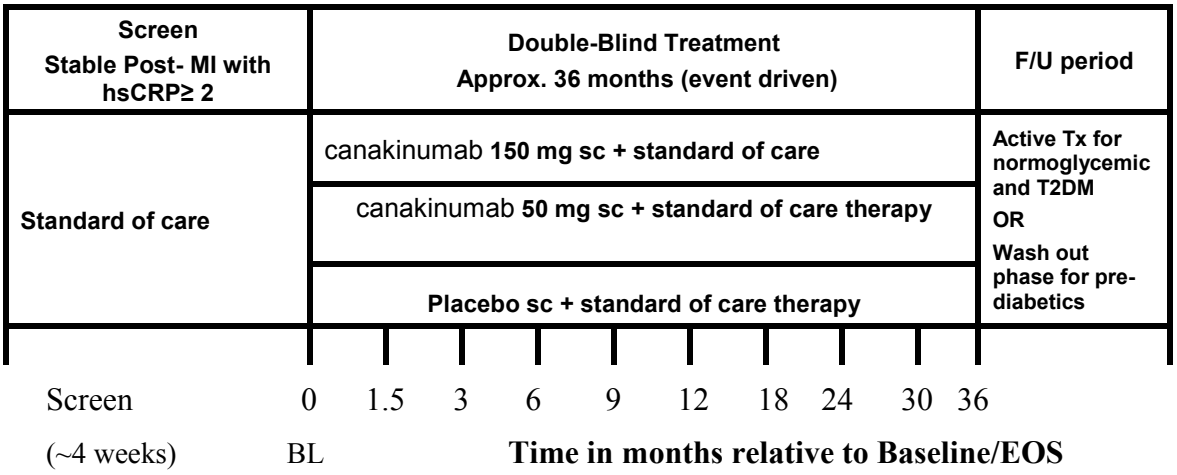
All patients who suffer a stroke during the double-blind period will participate in the, Post-Stroke Functional Assessment Sub-Study, see Section 6.6.3 for further details.

Interim Analysis

Interim analyses will be conducted for this trial; please Sections 3.5 & 9.8 for details.

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Figure 3-1 Study design



Months 15, 21, 27 & 33 are drug dispensing visits only and therefore not displayed

3.2 Rationale of study design

This study has been designed as a multi-center, randomized, parallel group, placebo-controlled, double-blind, event-driven trial to provide definitive evidence on the effects of canakinumab on cardiovascular adverse events in patients with recent MI and elevated inflammatory burden as evidenced by elevated hsCRP. This study will also measure the effects of canakinumab on the conversion to NOD as a secondary endpoint. This study design is the most robust clinical trial design to test the hypothesis that anti-inflammatory treatment with canakinumab will reduce major adverse cardiovascular events.

3.3 Rationale of dose/regimen, duration of treatment

Canakinumab doses were determined based on the results of studies CACZ885A2213 and CACZ885I2202. Results from these studies showed that canakinumab doses from 5 mg to 150 mg monthly were active in reducing hsCRP, used as marker for biological activity of canakinumab. The maximum efficacy in hsCRP lowering in study CACZ885I2202 was at approximately 50 -75 mg of canakinumab monthly. All canakinumab doses were safe and well tolerated and did not show any adverse lipid effects. Therefore, 50 mg monthly as fully efficacious dose and 15 mg monthly as submaximal dose were selected for further development. Optimal dosing interval was examined using data from CACZ885A2213 and from gout studies with canakinumab data on file. Modeling and simulation methods showed that 150 mg and 50 mg quarterly doses had similar IL-1β suppression to 15 and 50 mg monthly doses respectively. The doses and regimens were compared based on both the time for maintenance of suppression and the fraction of patients below a specified suppression threshold of "tissue free" IL-1β. Therefore, quarterly doses of 50 mg and 150 mg canakinumab were selected for this trial.

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3.4 Rationale for choice of comparator

This trial is placebo controlled to provide robust evidence on the effects of canakinumab on clinical events and safety as well tolerability. No comparative anti-inflammatory treatment has been shown to date to benefit patients with cardiovascular disease and thus an active comparator arm is not available. All patients in all treatment arms will receive standard of care post-MI background therapy including, but not limited to, lipid lowering, anti-hypertensive, beta blockers, and anti-platelet therapy as appropriate. High dose statin comparator therapy was initially considered as an appropriate active comparator; however, it was felt that it would be unethical to restrict use of proven benefit high dose statin therapy to the comparator arm only.

3.5 Purpose and timing of interim analyses/design adaptations

Interim analyses (IA) of efficacy, futility and safety will be carried out during the study in order to avoid exposing study patients to ineffective treatment or undue risks or to allow study discontinuation in case of overwhelming efficacy. Two interim analyses of efficacy will be performed when approximately 50% of the target number of patients with primary endpoints have been accumulated and the second one when approximately 75% of the planned number of patients with primary endpoints are available.

Interim analyses for futility will be conducted simultaneously with the analyses of efficacy. The criteria for formal statistical significance at the interim analyses are specified in the data analysis Section of the protocol, but details on futility boundaries and stopping rules will be pre-specified in the charter of the Data Monitoring Committee (DMC). The timing and number of safety analyses will also be specified in DMC charter, but these are estimated to occur on a six-month basis.

The unblinded results of the interim analyses will be reviewed by the DMC. Investigators, Novartis, and others who are involved in the conduct of the trial, in the analysis of the final trial results, or who have contact with study centers, will remain blinded to the treatment codes and interim analysis results until all monitoring decisions have been made and the database has been locked for final analysis.

The first interim analysis for efficacy will also include T2DM related glucose control data (exploratory endpoint parameters HbA1c, FPG and HOMA) only in patients with a diagnosis of T2DM at randomization. The unblinded results of the first interim analysis on T2DM related glucose control data will be reviewed by the DMC. These results will be shared with a senior Novartis representative, the Global Head of the CVM Franchise, and Senior Management for the purpose of planning canakinumab development outside this trial and CV indications. Study team and anyone with direct contact with study sites or involved with study assessments or monitoring will be kept blinded for these results.

4 Population

Participants eligible for this trial will include male and non-child-bearing potential female patients age 18 years and older who (a) have suffered a documented acute myocardial infarction at least 30 days before randomization and (b) have persistent evidence of systemic inflammation on the basis of an hsCRP $\geq$ 2 mg/L despite the use of standard of care post-MI

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medical therapies. Standard of care post-MI background therapy includes, but is not limited to, lipid lowering, anti-hypertensive, beta blockers, and anti-platelet therapy as appropriate.

In data from the PROVE IT – TIMI 22 trial, 43 percent of a post-MI population screened at 30 days had hsCRP ≥2 mg/L despite maximal therapy including high-dose statin (Ridker et al 2005).

In previous registries and studies of post-MI patients, approximately 25 percent are likely to have a diagnosis of T2DM, 35 percent are likely to be pre-diabetic, and 40 percent are likely to be normoglycemic patients. In this trial the following definitions of pre-diabetes and type 2 diabetes at randomizations will be used:

Definition of randomization Pre-Diabetes

- At visit 1 OR 2: HbA1c of 5.7-6.4% (ADA 2010 Clinical Practice Recommendations)

Definition of randomization Type 2 Diabetes

- At Visit 1 (screening) and Visit 2 (Randomization/Baseline) any patient with:
  - Medical history of type 2 diabetes and any patient currently on concomitant anti-diabetic medication

    or
  - HbA1c ≥6.5% (visit 1 and visit 2)

    or
  - FPG ≥ 126 mg/dL (visit 1 and visit 2).

    or
  - Combination of FPG ≥ 126 mg/dL and HbA1c ≥6.5% (visit 1 and visit 2)

The trial will be an event-driven global trial conducted in the outpatient setting. It is anticipated that approximately 694 cardiovascular endpoints will accrue during the course of the trial (see Section 9.7 for Power Calculations). To accomplish this goal, it is expected that around 14,600 patients will need to be screened in order to randomize approximately 7,302 patients.

4.1 Inclusion criteria

Patients eligible for inclusion in this study must fulfill all of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Male, or Female of non-child-bearing potential
3. Age ≥ 18 years at Visit 1.
4. Documented spontaneous MI (diagnosed according to the universal MI criteria with or without evidence of ST segment elevation) at least 30 days before randomization. (Thygesen et al 2007)
   - Diagnosis of prior MI should be based on medical history of clinical symptoms consistent with myocardial ischemia associated with elevation of cardiac biomarkers above the 99th percentile of the upper reference limit (preferably troponin) OR development of new pathological Q waves regardless of symptoms (see Appendix 3:

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ECG changes associated with prior myocardial infarction (Thygesen et al 2007). For details refer to the Universal Definition of MI (Thygesen et al 2007). Patients with MI resulting from PCI or CABG will not be eligible

5. Have an hsCRP ≥ 2 mg/L at screening (Visit 1) (which is at minimum of 28 days after qualifying MI or after any PCI performed separately from qualifying MI) on stable (at least 4 weeks) long term medications.

4.2 Exclusion criteria

1. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/ml)
2. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, UNLESS they are
   a. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/ml (for US only*:* and estradiol < 20pg/ml) or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.
3. Any of the following concomitant conditions or diseases:
   a. Planned coronary revascularization (PCI or CABG) or any other major surgical procedure.
   b. Major non-cardiac surgical or endoscopic procedure within past 6 months to Visit 1
   c. Multi-vessel CABG surgery within the past 3 years
   d. Symptomatic patients with Class IV heart failure (HF) (New York Heart Association [NYHA].
   e. Uncontrolled hypertension (defined as an average SBP >160 mmHg or an average diastolic blood pressure (DBP) >100 mmHg at Visit 1. Patients are allowed to be re-evaluated, at the discretion of investigator for this criterion if anti-hypertensive therapy has been started or increased as a result of initial screening blood pressure above these limits. (Mancia et al 2009).
   f. Uncontrolled diabetes as defined by the investigator
   g. Nephrotic syndrome or eGFR < 30 mL/min/1.73 m^2 per MDRD formula or kidney transplant (regardless of renal function), at Visit 1
   h. Known active or recurrent hepatic disorder (including cirrhosis, hepatitis B and hepatitis C, or confirmed alanine aminotransferase/ aspartate aminotransferase (ALT/AST) levels > 3 times ULN or total bilirubin > 2 times ULN) ,Visit 1
   i. Prior malignancy other than basal cell skin carcinoma
4. A history of alcohol and/or substance abuse that could interfere with the conduct of the trial

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5. History or evidence of active tuberculosis (TB) infection at Visit 1 or one of the risk factors for tuberculosis such as but not limited or exclusive to:
   a. History of any of the following: residence in a congregate setting (e.g. jail or prison, homeless shelter, or chronic care facility), substance abuse (e.g. injection or non-injection) health-care workers with unprotected exposure to patients who are at high risk of TB or patients with TB disease before the identification and correct airborne precautions of the patient

      or

   b. Close contact (i.e. share the same air space in a household or other enclosed environment for a prolonged period (days or weeks, not minutes or hours)) with a person with active pulmonary TB disease within the last 12 months.
6. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection, at Visit 1, determined as defined by local guidelines/ local medical practice (see also below for determination of tuberculosis status). If presence of tuberculosis is established then treatment (according to local guidelines) must have been completed prior to randomization.
7. Patients with suspected or proven immunocompromised state, including (a) those with evidence of Human Immunodeficiency Virus (HIV) infection; Patients on anti-retroviral therapy are excluded (b) those with any other medical condition which in the opinion of the investigator places the patient at unacceptable risk for participation in immunomodulatory therapy; or (c) those requiring systemic or local treatment with any immune modulating agent in doses with systemic effects e.g. high dose oral steroids. Topical, inhaled, local steroid use in doses that are not considered to cause systemic effects are permitted.
8. Live vaccinations within 3 months prior to the randomization visit or live vaccinations planned during the trial.
9. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.
10. Patients who have received an investigational drug or device within 30 days (inclusive) of Visit 1, or who are expected to participate in any other investigational drug or device study during the conduct of this trial, except for patients who have an investigational treatment eluting stent (DES), provided that they have completed the DES trial. FDA/country-specific drug regulatory authority approved DES devices are permitted.
11. Any biologic drugs targeting the immune system (for example, TNF blockers, anakinra, rituximab, abatacept, tocilizumab)
12. Any life threatening condition with life expectancy < 5 years, other then vascular disease that might prevent the patient from completing the study

Determination of tuberculosis status

Determination of tuberculosis status will be required before administration of study drug and should be performed as defined by local guidelines. Patients need to have given written informed consent before any of these assessments are initiated. Patients who have had any one of the below assessments performed within 30 days of screening, Visit 1, will not need

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repeat testing performed to determine eligibility. All other patients will need tuberculosis status determined at Visit 1. .

Any significant findings will be recorded in the "Medical History" Section of the eCRF as necessary

Patients with either a positive PPD or QFT-g test may still participate in the study if

1. Treatment (according to local guidelines) has been completed prior to randomization

or

2. Further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis.

PPD skin test

A PPD skin test may be initiated to evaluate for an occult infection with TB. The test dose is bioequivalent to 5 tuberculin units (or as according to local standard practice) of standard PPD usually injected intradermally into the volar surface of the forearm. The injection site will be cleansed and the PPD extract will then be injected into the most superficial layer under the skin. If given correctly, the injection should raise a small wheal of about 5 mm, which resolves within 10-15 minutes.

A reaction will be measured in millimeters of indurations (hard swelling) after 48h – 72h. A PPD skin induration > 5 mm is interpreted as positive result. This will determine whether the patients have had a significant reaction to the PPD skin test.

The investigator will either obtain PPD skin tests on his own and be reimbursed by Novartis for its cost or be supplied with them by the Novartis affiliate, depending on the local Novartis policy.

QuantiFERON-TB Gold assay

A QuantiFERON®-TB Gold assay may be performed to assess the TB status at baseline on patients as needed.

This blood-based assay is specific for Mycobacterium tuberculosis and is not influenced by previous Bacillus Calmette-Guérin vaccination or exposure to other Mycobacteria species. This test, in contrast to the PPD skin test, is also insensitive to a booster effect since the patient is not exposed to the vaccine. The assay measures the production of interferon-gamma and puts it into relation to a negative and a positive control sample.

QuantiFERON®-TB Gold samples will be processed by the central lab.

Details about sample processing are described in the central laboratory manual.

Chest x-ray

A chest x-ray may be performed if required by local regulations in case of positive PPD skin test or QuantiFERON-TB Gold® assay.

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If in line with local guidelines/ local medical practice, a chest x-ray only will be sufficient to check eligibility with respect to TB status prior to randomization. This x-ray should be no more than 30 days old at the time of screening.

5 Treatment

5.1 Investigational and control treatment

Canakinumab (ACZ885) or matching placebo solution for injection will be provided by Novartis as ready-to-use pre-filled syringes. The sites will receive their first shipment of study treatment only after the first screened patient has been registered in the IVRS/IWRS. Two strengths will be supplied: Canakinumab 150 mg in 1 mL solution for injection and canakinumab 50 mg in 0.5 mL solution for injection, as well as, two placebo formulations matching to the two active drug formulations. The study drug will be given as a quarterly subcutaneous injections starting immediately after randomization. The two quarterly study treatment injections (double dummy design one syringe of 1 mL and one syringe of 0.5 mL) will be administered at study sites by trained site staff, facilitating both compliance and long-term follow-up for both safety and efficacy outcomes. The doses are canakinumab 150 mg quarterly and canakinumab 50 mg quarterly. Study treatment and placebo will be given in addition to local standards of care for post-MI patients which may include lipid lowering, anti-hypertensive, beta blockers and anti-platelet therapies and is determined by the responsible physician. The sites should make alternative arrangements for those patients likely to miss visits due to travel or other reasons to be seen in an alternative study site.

No study treatment will be provided for those pre-diabetic patients at their final visit and during the 6 month washout period.

5.2 Treatment arms

Patients will be assigned to one of the following 3 treatment arms in a ratio of 1:1:1

- Canakinumab 50 mg quarterly subcutaneous
- Canakinumab 150 mg quarterly subcutaneous
- Placebo

5.3 Treatment assignment

At Visit 2 all eligible patients will be randomized via Interactive Voice Response System /Web System (IVRS/IWRS) to one of the treatment arms. The investigator or his/her delegate will contact the IVRS/IWRS after confirming that the patient fulfills all the inclusion/exclusion criteria. The IVRS/IWRS will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the patient. The randomization number will not be communicated to the caller.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IVRS/IWRS provider using a validated system that

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automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to study drug packs containing each of the study treatment.

Stratification

Randomization will be stratified by 'time since most recent MI' as follows:

- 50% Post MI ≥ 30 days but < 6 months
- 50% Post MI ≥6 months

Sites will be asked to indicate the patients' glycemic status at the first call post randomization as the V2 lab results are needed for the following categories (see Section 3.1 for definitions):

- Normoglycemia HbA1c <5.7% at V1 or V2
- Pre-Diabetes : HbA1c 5.7 – 6.4 % inclusive, as confirmed at V1 & V2
- T2DM : HbA1c ≥ 6.5% OR FPG ≥ 126 mg/dL OR combination of HbA1c and FPG as confirmed at V1 & V2

Sites are required to call the IVRS at every visit to:

- Visit 1: Register the screening visit. The first shipment of study treatment will ONLY be sent once the site registers their first screened patient.
- Visit 2: Register Screen Failures or randomize a patient
- Visit 3: Register the occurrence of the visit
- Obtain medication numbers for quarterly dispensing of study treatment
- Register a patient who has died or withdrawn consent
- Register a patient who has completed (this will only occur when the study has been deemed complete by the DMC or Novartis and the patient returns for the EOS visit.)

The randomization scheme for patients will be reviewed and approved by a member of the IIS

Biostatistics Quality Assurance Group. The randomization codes will be maintained at Center for CV Prevention, Brigham and Woman's Hospital, Harvard School of Medicine

5.4 Treatment blinding

Patients, investigator staff, persons performing the assessments, and data analysts will remain blind to the identity of the treatment from the time of randomization until database lock, using the following methods:

Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the exception of the independent unblinded statistician, programmer and data manager/data coordinator (and assistant as required), who need to have access to prepare safety and efficacy interim analysis reports for the DMC. These personnel will not be involved in any other trial activities.

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The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration and appearance.

The first two study medication injections received for the open label safety follow up study (at the main study EOS visit) will be blinded in order to keep blinding intact during study closeout phase and database lock

Unblinding will only occur in the case of patient emergencies (see Section 5.5.9) at the time of interim analysis and at the conclusion of the study. In the event a patient becomes unblinded for any reason they may continue study treatment and assessments according to the protocol at the discretion of the investigator.

PK, biomarkers, immunological laboratory and canakinumab antibody results will be blinded to the sites and Novartis but will be available unblinded for the DMC analyses to assure patient safety.

5.5 Treating the patient

5.5.1 Patient numbering

Each patient is uniquely identified in the study by a **Patient Number**. A center number is also assigned by Novartis to the investigative site. Upon signing the informed consent form, the patient is assigned the next sequential patient number by the investigator. The investigator or his/her staff will contact the IVRS/IWRS and provide the requested identifying information for the patient to register them into the IVRS/IWRS. In the electronic data capture (EDC) system, there will be blank CRF books available labeled with a Patient Number. The site should select the CRF book with a matching Patient Number to enter data.

Once assigned to a patient, the Patient Number will not be reused. If the patient fails to be randomized for any reason, the IVRS/IWRS should be notified within 2 days that the patient was not randomized. The reason for not being randomized will be entered on the Screening Period Phase Disposition eCRF.

5.5.2 Dispensing the study treatment

Each study site will be supplied by Novartis with study treatment in packaging of identical appearance. The first shipment of study treatment will occur once the site has registered their first screened patient in the IVRS/IWRS. All injections should be administered by the site staff only.

The study treatment packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the 4 formulations provided (two active and two placebo forms). Investigator staff will identify the two study treatment packages for the patient at each quarterly (every 3 months) dosing visit by contacting the IVRS/ IWRS and obtaining the medication numbers. Immediately before administering the study treatment, the, investigator staff will detach the outer parts of the labels from the packaging and affix them to the source document (Drug Label Form) for that patient's unique patient number.

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5.5.3 Supply, storage and tracking of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Upon receipt, all study treatment should be stored in the refrigerator according to the instructions specified on the drug labels. Clinical supplies are to be dispensed only in accordance with the protocol.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug and no information about the patient.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability ledger. Monitoring of drug accountability will be performed by the field monitor during site visits and at the completion of the trial.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability ledger to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

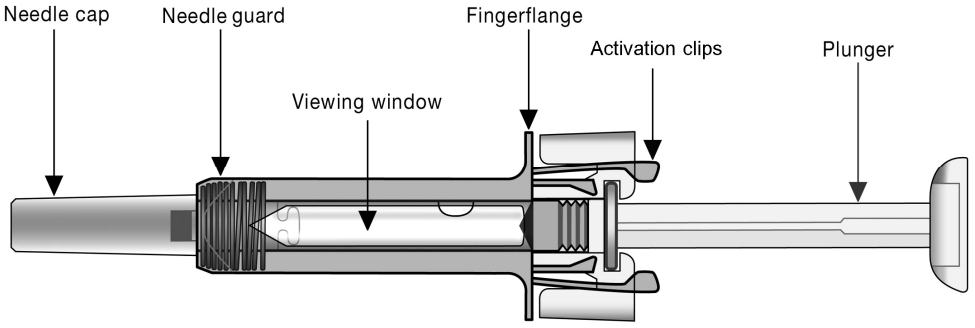
5.5.4 Instructions for prescribing and taking study treatment

Canakinumab syringe

Before using the syringe, please read the following information carefully.

The pre-filled syringes are individually sealed in a plastic tray.

Parts of the pre-filled syringe



Important Safety Information

1. Be careful not to touch the device activation clips (see illustration above) at any time. By touching them, the safety device may self-activate.
2. Do not remove the needle cap until just before you give the injection.
3. The syringe cannot be re-used. Dispose of the used syringe immediately after use into a sharps container.

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Storage of the pre-filled syringe

1. Store the syringe in a refrigerator, sealed in its plastic tray according to the labeled storage condition.
2. Do not use the syringe after the expiration date shown on the outer box or syringe label.

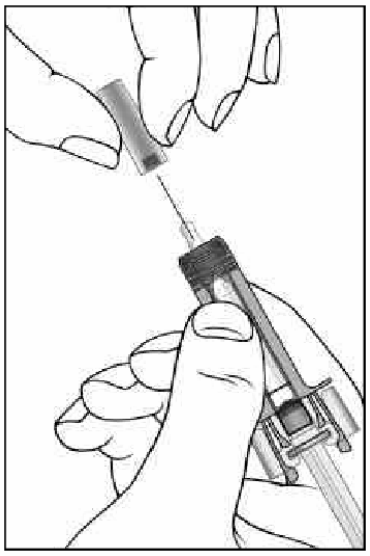
Preparing the syringe for use

Warning: Prior to completion of the injection, avoid contact with the device activation clips (see first illustration) to keep it from prematurely covering the needle with the needle guard.

1. Remove the plastic tray containing the syringe from the refrigerator. Do not uncover the plastic tray.
2. Allow the tray to come to room temperature (approximately 20 minutes)
3. Peel back the paper cover from the plastic tray, and remove the syringe.
4. Inspect the syringe. DO NOT USE if it is broken or if the liquid looks cloudy or contains particles. The air bubble in the syringe is normal. You do not have to expel any air before use.

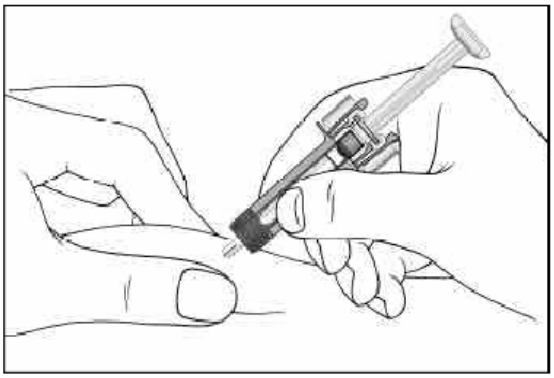
How to use the syringe

Step 1: Hold the syringe vertically with the needle cap up and carefully remove the needle cap from the syringe. Discard the needle cap. Do not touch the needle after the cap is removed.

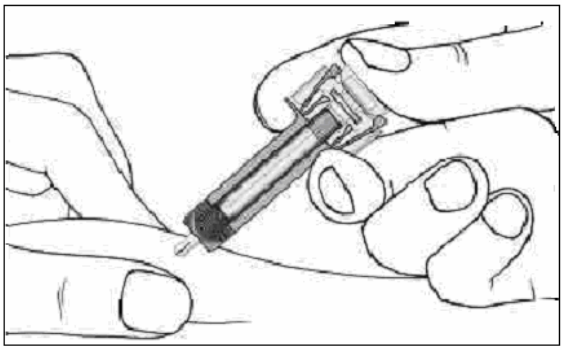


Step 2: Gently pinch the skin at the injection site. Insert the needle.

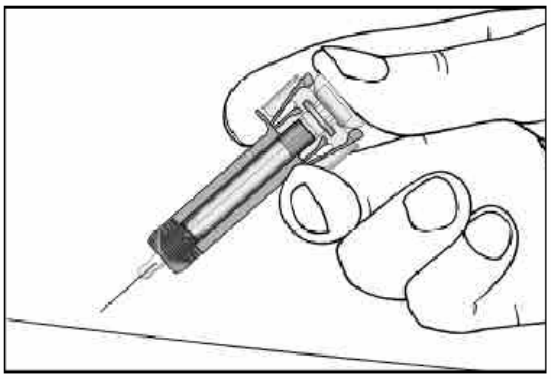
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Step 3: Holding onto the finger flange, slowly press the plunger all the way down until all the drug is injected.

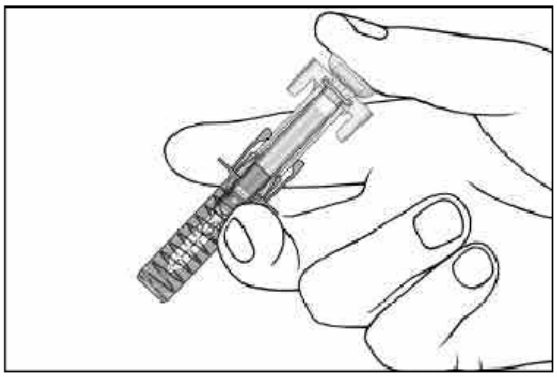


Step 4: After the complete dose is given, hold the syringe in place for 5 seconds to allow the drug to distribute in the tissue. Then, by holding the plunger down, remove the needle from the skin.



Step 5: Slowly release the plunger and allow the needle guard to automatically cover the exposed needle.

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NOTE: If the needle guard does not extend automatically, firmly push on the plunger. Then release the plunger and allow the guard to cover the needle.

Step 6: Dispose the used syringe immediately into a sharps container.

All randomized patients, starting at Visit 2 will receive two quarterly subcutaneous injections. Patients will receive either one injection of canakinumab and one injection of placebo, or two injections of placebo. Injections will be given after all other study assessments have been completed for the visit. All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF. All drug kits assigned by the IVRS/IWRS will be recorded/databased in the IVRS/IWRS. The investigator should promote compliance by informing the patient that compliance is necessary for the patient's safety and the validity of the study.

Principal investigator or trained staff will select injection site(s) for the study injections which may be administered subcutaneously in the abdomen and/or extremities.

5.5.5 Permitted dose adjustments and interruptions of study treatment

For patients who are unable to tolerate the protocol-specified dosing scheme, dose interruptions are permitted in order to keep the patient on study treatment. Patients are encouraged to continue study treatment; however, patients are allowed to interrupt and re-start medication at any time during the study at the discretion of the investigator.

These changes must be recorded on the Dosage Administration Record CRF (eCRF).

5.5.6 Concomitant treatment

The investigator should instruct the patient to notify the study site about any new medications he/she takes after signing the informed consent. All medications and significant non-drug therapies (including physical therapy and blood transfusions) taken within 30 days of screening and administered after the patient has signed informed consent must be listed on the appropriate Concomitant Medications and or Procedures and Significant Non-Drug Therapies eCRF.

Patients who are on warfarin or warfarin like treatment with narrow therapeutic index should have their international normalized ratio (INR) measured locally and warfarin or warfarin like treatment dose adjusted accordingly within one month from starting study treatment. This is a general precautionary measure because canakinumab is not expected to interact with warfarin.

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5.5.7 Prohibited treatment

Use of any treatments below are NOT allowed after the start of study treatment due to potential increase in immunosuppressant related concomitant conditions. They are prohibited for the duration of the study and for at least 90 days after discontinuation of study treatment.

If a patient chooses to continue one of the medications above they would still be required to be followed as per protocol to assess for any potential study endpoints. If a patient stops taking any of the below prohibited medications they are eligible to restart study treatment 90 days after stopping the prohibited medication, at the discretion of the investigator.

- Any anti retro-virals and / or any biologic drugs targeting the immune system (e.g., TNFα blockers, anakinra, rituximab, abatacept, tocilizumab)
- immune suppressive drugs :e.g. high dose systemic oral steroids

5.5.8 Discontinuation of study treatment and premature patient withdrawal

The investigator should discontinue study treatment for a given patient if, on balance, he/she believes that continuation of study treatment would be detrimental to the patient's well-being. If any patient discontinues study treatment, the site is required to follow the patient, as per the study assessment schedule (either by phone or on site visits) until the site has been notified by Novartis that the study has been deemed complete.

Study treatment *must* be discontinued under the following circumstances;

- Withdrawal of informed consent. Study treatment may only be resumed if the patient has re-consented to participation
- Pregnancy, patient must discontinue study treatment if pregnant; however they can resume participation in the study after stopping breast feeding.
- Use of prohibited treatment as per Section 5.5.7
- Any other protocol deviation that results in a significant risk to the patient's safety

Any of the following laboratory abnormalities

Clinical Symptoms as noted below, without regard to Liver Function Test's (LFT)

- A jaundice like event
- Any serious adverse event (SAE) indicative of fatal or non fatal hepatitis, liver failure or its complications

LFT elevations and Clinical Symptoms

- ALT or AST > 3X ULN
- Clinical symptoms suggestive of hepatic dysfunction – such as general malaise, fatigue, abdominal pain, nausea, vomiting or rash with eosinophilia

Asymptomatic elevations of ALT / AST /T. Bilirubin

- ALT or AST > 3x ULN with a T. Bilirubin > = 2x ULN

Asymptomatic isolation of elevations of ALT or AST

- ALT or AST > 8 x ULN discontinue study treatment if elevation persists > 48 hrs

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- ALT or AST ≥ 5x ULN < 8x ULN discontinue study treatment if elevation persists > 2wks.
- ALT or AST≥ 3x ULN <5 ULN discontinue medication at the discretion of the investigator

Asymptomatic isolation elevation of T. Bilirubin

- T. Bilirubin ≥ 3x ULN discontinue if elevation persists > 2 wks

Study treatment may be restarted at the discretion of the investigator, if the reason for withdrawal of study treatment has resolved. Every effort should be made to restart study treatment, if deemed appropriate by the investigator(s)

The appropriate personnel from the site and Novartis will assess whether study treatment should be discontinued for any patient whose treatment code has been broken inadvertently for any reason.

Patient Status

Patients may voluntarily withdraw from the study for any reason at any time; however, they must be reminded that the site will attempt to obtain a vital status yearly and at the conclusion of the trial to assess for any potential study endpoints.

Study Treatment Discontinuation: If premature discontinuation of study treatment occurs for any reason, the investigator must make every effort to determine the primary reason for a patient's premature discontinuation from the study. Patients who discontinue study treatment should NOT be considered withdrawn from the study. For any patient who chooses to discontinue study treatment, the site must capture this information on the Drug Accountability Record eCRF. The site must contact the patient as per the assessment schedule as every effort must be made by sites staff to follow patients for cardiovascular events and health status. It is at the discretion of the investigator if the patient is to return to the clinic for regular visits or be contacted by telephone. If at the end of study, contact is made to the patient (or on site visit) to assess a health status; the patient will be deemed "completed".

Lost to-Follow-up: Sites must make every effort to reach patients who fail to return for visits, or become lost to follow-up for any reason, as all patients must be accounted for, at the EOS, to assess for study endpoints. The investigator must show "due diligence" by documenting in the source documents the steps taken to contact patients who are lost to follow-up (i.e. those patients whose life or death status is unclear because they fail to appear for study visits without stating an intention to withdraw). Steps taken include dates of telephone calls, registered letter confirmations, and etc. Sites will be requested to complete the Visit Information eCRF at the regularly scheduled study timepoints to document the attempts made to contact a person. "Lost to Follow Up information will be captured on the Study Phase Completion eCRF only if sites are unable to obtain a status on a patient at the end of the study. It is permissible for a patient to contact the site to return for a scheduled clinic visit, at which time their status should then be updated in the systems appropriately. Patient will maintain the previously provided Patient Number and resume study activities based upon their original randomization date.

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Withdraw Consent: Any patient who withdraws their consent to participation of study procedures will have this information captured on the Study Phase Completion eCRF which will prompt annual completion of the Survival Information eCRF. To complete the Survival Information page; sites will be asked to check public registries on an annual basis to try and obtain a health status on their patients. Patients may re-consent at any time to resume their participation in the trial. Patients will maintain the previously provided Patient Number and resume study activities based upon their original randomization date.

Patients who discontinue study treatment prematurely will not be replaced by an equal number of newly enrolled patients.

5.5.9 Emergency unblinding of treatment assignment

Emergency unblinding should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency code breaks are performed using the IVRS/IWRS. When the investigator contacts the system to unblind a patient, he/she must provide the requested patient identifying information and confirm the necessity to unblind the patient. The investigator will then receive details of the drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the Clinical Trial Head that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IVRS/IWRS in case of emergency. The investigator will inform the patient how to contact his/her backup in cases of emergency when he/she is unavailable. The investigator will provide protocol number, study treatment name if available, patient number, and instructions for contacting the local Novartis Country Pharma Organization (CPO) (or any entity to which it has delegated responsibility for emergency code breaks) to the patient in case emergency unblinding is required at a time when the investigator and backup are unavailable.

Any patient who is unblinded will continue in the study and may continue medication as per protocol.

5.5.10 Study completion and post-study treatment

The study closeout will be initiated once the study has reached its primary endpoint of 694 primary CV events. At this time point sites will be notified to bring back all study patients for a final EOS visit. It is at this time patients who have an EOS status obtained will be deemed completed. At this time, any patient who has signed the informed consent, but has not been randomized into the trial will not be eligible to proceed to randomization and should be registered as a screen failure.

Once the study is deemed successfully completed (694 primary CV events reached) or is stopped by the DMC recommendation of overwhelming efficacy (prior to 694 primary CV events reached) or Novartis the following will take place

- All patients with a glycemic status of pre-diabetes will proceed into the 6 month washout phase

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- All other patients will continue into an open label extension until such time that study drug is approved for marketing and is available for prescribing physicians and a registry study is approved by local regulatory agencies. At this final open label extension visit, these patients will receive their injections from the sites. The open label extension is then deemed complete and the patient enrolled into the registry study.
- All patients with a glycemic status of pre-diabetes who completed the 6 month wash-out phase will restart study treatment at the end of the washout phase and will continue on to the open label extension phase as noted above.

5.5.11 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, patients should be seen as soon as possible and treated as described in Section 6. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 lists all of the assessments and indicates with an "x" when the visits are performed. Patients should be seen for all visits on the designated day or as close to it as possible. The study assessment schedule below outlines all procedures performed on patients at scheduled visits. The administration of study treatment is performed quarterly at study sites by trained site staff after the completion of all other assessments.

The visit assessments listed below are for the estimated timeframe a patient would participate in the study. This is an event driven trial and will be stopped when the target number of primary cardiovascular endpoints have been accrued (please see Section 9 for details). All patients will continue study treatments and visits until the event target has been reached. Patients who complete the 36 months will still be required to return to the clinic every 6 months for study assessments and quarterly for study treatment until notified by the site staff of trial completion. Only when the site staff has been notified of the trial completion by Novartis will the patients with a glycemic status of pre-diabetic be asked to enter the 6 month washout phase at their EOS visit.

Patients should attend visits, where labs are drawn, in a fasting state of 10 hours

Pre-screenin is a key element to successfully identifying the correct patients to be screened for this clinical study. All patients should have an available hsCRP value prior to the time of screening. The available hsCRP value should be at least 28 days after a cardiovascular event or procedure or major surgical procedure, and must be less than 60 calendar days prior to screening. The Pre-screening visit should be used after review of the patients charts to determine patients eligibility and to obtain an hsCRP value, which is to be run locally, for those potentially eligible patients who do not have one available.

Converting to T2DM: Any patient who is reported as having an elevated HbA_{1c} of FPG as defined in Section 3.1, will need to have an unscheduled visit within 6 weeks following the first result to assess for conversion from pre-diabetes to T2DM.

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Deterioration in Glycemic Control in T2DM Patients: Any patient who is reported as having an elevated $HbA_{1c} \geq 7.5\%$ as defined in Section 6.6.1 , will need to have an unscheduled visit within 6 weeks following the first result to confirm the HbA1c $\geq 7.5\%$.

Discontinuation of study treatment: It is highly encouraged that patients who discontinue study treatment to still attend regularly scheduled clinic visits. If the patient does not attend the scheduled visit, site staff are required to make a telephone contact with the patient to assess for any potential study endpoints and record as appropriately in the eCRFs.

Withdrawal of consent or Lost to Follow-Up: Sites are required to provide an annual update in the eCRF's for any patient who has a status of Withdrawal of consent. Please see Section 5.5.8 For any patient who fails to appear for on site visits the study staff will be required to complete the Visit Information eCRF .

For any patients who suffer from a stroke during the trial please see Section 6.6.4 for details

Sites are required to call the IVRS as the screening visit and at each visit to register their patient's status and if applicable, receive the medication numbers to dispense treatment. Dispensing of medication should be the last assessment performed at each visit.

Table 6-1 Assessment schedule

Visit	Pre Screen	1	2	3	4	5	6	7	8	9	10	11	12,16	13,17 [10]	14,18 [10]	15,19 [10]	End of Study (EOS)	End of pre-diabetes washout[5]
Month		-½	**0**	**1.5**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27,39.**	**30,42..**	**33,45.**	**36,48.**	**event driven**	**EOS + 6 months**
Obtain informed consent		X																
Prescreening Informed Consent	X																	
Height		X																
Inclusion/Exclusion		X																
Labs for entry criteria only:, HIV Screen, HBsAg and HCV antibody		X																
Hs-CRP	X[9]	X	X	X	X		X	X		X		X		X		X	X	X
Determination of tuberculosis status[1]		X																
Demography																		
Demography		X																
History of CV Disease		X																
Medical History/Current Conditions		X																
Family History of CV disease			X															
Smoking& Alcohol History			X															

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Visit	Pre Screen	1	2	3	4	5	6	7	8	9	10	11	12,16	13,17 [10]	14,18 [10]	15,19 [10]	End of Study (EOS)	End of pre-diabetes washout[5]
Month		-½	**0**	**1.5**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27,39..**	**30,42..**	**33,45..**	**36,48...**	**event driven**	**EOS + 6 months**
Treatment Assessments																		
Call IVRS		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug Dispensing			X		X	X	X	X	X	X	X	X	X	X	X	X	X[6]	X[6]
Prior & Concomitant Antidiabetic & CVD Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Assessments																		
Potential endpoint assessment				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HbA1c & FPG (all patients)[2]		X	X	X	X	X	X	X		X		X		X		X	X	X
Safety Assessments																		
Physical Exam (including weight)			X					X				X				X	X	X
Vitals(includes BMI)		X	X	X	X	X	X	X		X		X		X		X	X	X
ECG			X					X				X				X	X	X
Standard Hematology & Chemistry		X	X	X	X	X	X	X		X		X		X		X	X	X
Fasting Lipid Profile[3]		X	X	X	X	X	X	X		X		X		X		X	X	X
Other Biomarkers[4]			X		X			X									X	
Immunological (e.g. ANA) Screen			X														X	
Immunogenicity (Anti- canakinumab Ab)			X	X	X			X		X							X	X
canakinumab (PK)			X	X	X			X		X							X	X
IL-1β			X	X	X			X		X							X	X
Urinalysis including albumin/creatinine ratio (in patients with T2DM or pre-diabetes at baseline)			X		X			X						X			X	X
AE (prompting for infections)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test in women			X														X	

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Visit	Pre Screen	1	2	3	4	5	6	7	8	9	10	11	12,16	13,17 [10]	14,18 [10]	15,19 [10]	End of Study (EOS)	End of pre-diabetes washout[5]
Month		-½	**0**	**1.5**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27,39...**	**30,42..**	**33,45...**	**36,48....**	**event driven**	**EOS + 6 months**
Other																		
Pharmacogenetics & pharmacogenomics [8]			X															
EQ-5D			X		X	X		X								X	X	X
SF-36[7]			X	X	X	X	X	X										
MFSI-SF[7]			X	X	X	X	X	X										
Patient education and Counseling			X															

[1]Please see protocol Section 4.2_ Determination of tuberculosis status for details.

[2] Diagnosis of diabetes or failure of glycemic control based on HbA1c data (and/or FPG for diagnosis of diabetes) should be verified by a repeat HbA1c and FPG within 6 weeks of the initial observation.

[3] Patient must have fasted 10 hours for this test. [3]Triglycerides (TG), total cholesterol, HDL cholesterol, LDL cholesterol, VLDL cholesterol and non-HDL cholesterol. LDL Cholesterol, VLDL cholesterol and non-HDL cholesterol will be calculated unless triglycerides > 400 mg/dL in which case only a direct LDL cholesterol assay will be employed.

[4] A panel of biomarkers may include but are not limited to: IL-1Ra, IL-6, IL-18,leptin, adiponectin (total and high MW), TNFα, PAI-1 and fibrinogen

[5] Only patients with pre-diabetes status will enter into this washout period.

[6] Patients who consent to the long-term open-label safety extension will receive their injections at this end of study visit. All those “pre-diabetic” will not receive an injection at the end of study visit, but will enter the 6 month washout period and then enter the long-term open label safety extension thereafter.

[7] Please see Section 6.6.2 for administration of the questionnaires in addition to the use of the modified Rankin Questionnaire.

[8] Optional for patients and will not exclude them from study participation if declined but encouraged.

[9] Optional for sites to utilize if there is no documented hsCRPon file for the patient within the protocol specified timeline. This sample should be run locally by the investigator.

[10] This sequence of visits will repeat until the study is deemed complete and sites are notified by the Sponsor to have all patient return for the EOS assessments

6.1 Information to be collected on screening failures

All patients where informed consent has been given (including screening failures), will have the Study Phase Completion eCRF , demographics, inclusion / exclusion, informed consent page and SAE data collected.

For screened patients who signed informed consent but are not randomized or entered into the next epoch of the study (usually starting at visit 1) will have adverse events that are not SAEs followed by the investigator and collected only in the source data.

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For all patients who signed the informed consent and are randomized, or who are entered into the next epoch of the study, will have all adverse events occurring after informed consent recorded on the adverse event eCRF page, with the exception of all study endpoints.

The investigator will have the discretion to record abnormal test findings on the medical history eCRF whenever, in their judgment the test abnormality occurred prior to the informed consent signature. For example: an investigator can determine that an ECG abnormality that was seen on an ECG conducted after informed consent was obtained was a pre-existing condition. This pre-existing condition is then recorded on the medical history eCRF and not as an adverse event

6.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients include: information on date of birth (if allowable), age, sex, race and ethnicity.

Relevant medical history/current medical conditions present before signing informed consent will be collected at Visit 1. General medical history will include: HEENT, Neoplastic and Hematological Disorders, Cardiovascular history, including MI history, prior events or disease, hypertension, hyperlipidemia, smoking history, Respiratory, Kidneys and Urinary Tract, Gastrointestinal, Immunological and infectious, Endocrine and Metabolic including history and diagnosis of diabetes and it's complications, CNS including psychiatric disorders. Relevant medical history/current medical condition data includes data until signing of informed consent. Where possible, diagnoses and not symptoms will be recorded. Family history for cardiovascular diseases will be collected.

6.3 Treatment exposure and compliance

Study treatment will be administered at the clinic under the supervision of the investigative staff with the dosing record captured within each visit on the Drug Accountability eCRF.

Any medications taken within 30 days prior to the date of screening and after will be recorded on the appropriate Concomitant Medications and or Procedures and Significant Non-drug Therapies eCRF.

6.4 Efficacy

6.4.1 Primary Efficacy assessment (primary objective)

The primary endpoint is defined as the time to the first adjudication committee confirmed major adverse cardiovascular event (MACE) occurring during the double-blind treatment period, which is a composite of CV death, non-fatal MI, and stroke.

An independent adjudication committee that is blinded to treatment assignments will review and adjudicate all clinical events that constitute the primary composite endpoint and secondary endpoints.

6.4.2 Secondary efficacy assessment (secondary objectives)

Key secondary efficacy assessments will comprise:

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- Time to the first occurrence of the adjudication committee confirmed composite cardiovascular endpoint consisting of primary endpoint, and hospitalization for unstable angina requiring unplanned revascularization
- Time to adjudication committee confirmed new onset of type 2 diabetes among those with pre-diabetes at randomization (defined in Section 4) (time to NOD)

Other secondary efficacy assessments will comprise

- Time to first event of, non-fatal MI, stroke and all-cause mortality composite
- Time to all-cause mortality

Exploratory efficacy assessments will comprise

- Time to first event of total vascular events composite consisting of primary endpoint, hospitalization for unstable angina, or for any other non-coronary ischemic event (transient ischemic attack or limb ischemia), any revascularization procedure (coronary and non-coronary) and limb amputation
- Other cardiovascular disorders with a known inflammatory component:
    - Time to first deep vein thrombosis/pulmonary embolism
    - Time to first supraventricular tachycardia/atrial fibrillation
    - Time to first stent thrombosis (definite or probable)
    - Time to first hospitalization or prolongation of hospitalization for heart failure
    - Time to first major coronary event (CHD death or MI)
    - Time to first event of coronary revascularization procedures (PCI or CABG)
    - Time to first stroke by etiology
- Glycemic control among those with type 2 diabetes at randomization (defined in Section 4)
    - HbA1c , FPG, and anti-diabetic medication changes by visit from baseline. This analysis includes both longitudinal as well as categorical assessments using HbA1c, FPG, and diabetic medication changes from baseline.
- Failure of glycemic control analyses defined as HbA1c $\geq$ 7.5% (see Section 6.6.1)

Change from baseline in biomarkers of cardiovascular and diabetes risk, including nephropathy by albumin/creatinine ratio in patients with T2DM or pre-diabetes at baseline, inflammatory biomarkers, glycemic control markers, and β-cell function markers

- Change from baseline in patient reported outcomes of tiredness, physical function and performance function and in health status as assessed by the EQ-5D Quality of Life (QOL) assessment.
- Exploratory pharmacogenetic assessments to examine whether individual genetic variation in genes relating to drug metabolism, major cardiovascular event, type 2 diabetes, and the drug target pathway confer differential response to canakinumab.

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6.4.3 Appropriateness of efficacy assessments

Time to major adverse cardiovascular events and progression to diabetes (new onset diabetes) are well defined and standard clinical events in clinical trials aimed at demonstrating primary and secondary efficacy of investigational agents on clinical endpoints. Secondary endpoints are widely used clinical efficacy endpoints in cardiovascular clinical endpoint trials. Exploratory endpoints are hypothesis generating and exploratory in nature.

6.5 Safety

Safety and Tolerability Assessments

- Laboratory evaluations
- Weight
- Adverse events and serious adverse events, including cardiovascular events, malignancies, and infections
- Discontinuation due to AEs
- Hypoglycemia events
- Injection site reactions
- Physical Exam
- Biomarkers
- Vitals
- ECG

Serious allergies/immunological events (e.g. Anti-canakinumab antibodies), serious infections, and malignancies adverse events will be monitored carefully using adverse/serious adverse events procedure described in Section 7.1 Adverse events and Section 7.2 Serious adverse event reporting during this trial because these adverse events represent hypothetical mechanism of action related risks of canakinumab therapy. These adverse events will be adjudicated by an expert adjudication committee to strengthen data quality and safety conclusions.

6.5.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to signing of informed consent must be included in the relevant Medical History/Current Medical Conditions eCRF. Significant findings after the signing of informed consent which meet the definition of an Adverse Event must be recorded on the Adverse Event screen of the patient's eCRF.

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6.5.2 Vital signs

Vital signs including BP (3 measurements with the average of all three used for inclusion) and pulse measurements will be assessed at as per the assessment. In general blood pressure should be taken after the patient has been sitting for five minutes, with back supported and both feet placed on the floor. Systolic and diastolic blood pressure should be measured three times using an automated validated device with an appropriately sized cuff (for arm circumference of 27 to 34 cm, the cuff should be “adult” size: 16 X 30 cm, for arm circumference of 35 to 44 cm, the cuff should be “large adult” size: 16 X 36 cm, and for arm circumference of 45 to 52 cm, the cuff should be “adult thigh” size: 16 X 42 cm). The repeat sitting measurements should be made at 1 to 2 minute intervals and the mean of the last two measurements will be used. If using the automated devise and current cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

Clinically notable vital signs are defined in Appendix 1.

6.5.3 Height and weight

Height in centimeters (cm) or inches and body weight (to the nearest 0.1 kilogram [kg] or pound [lb] in indoor clothing, but without shoes) will be measured. Body Mass Index (BMI) will be calculated as the weight in kg divided by the height in meters, squared. Waist circumference should be measured with a flexible tape. For consistency among sites, the position for measuring waist circumference will be at the uppermost border of the right iliac crest (or at the umbilicus if landmarks cannot be palpated). The measure should be recorded while the patient is in the expiratory phase of respiration.

6.5.4 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual. All patients should be fasting for at least 10 hours prior to having the labs drawn at the scheduled time-points.

An additional sample will be sent to the Data and Laboratory Coordinating Center for long term storage. Upon completion of the study these samples will be analyzed for cardiovascular and metabolic biomarkers and genetic analysis, if prior written informed consent is obtained

Clinically notable laboratory findings are defined in Appendix 1.

6.5.4.1 Hematology

The following tests are included in the hematology but are not limited to: HbA1c, Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count will be measured.

6.5.4.2 Clinical chemistry

The following tests are included in the chemistry but are not limited to: hsCRP, eGFR, Estradiol, Fasting Plasma glucose, Blood urea nitrogen, creatinine, CK total bilirubin, AST, ALT, alkaline phosphatase, sodium, potassium, chloride, calcium, phosphorous, total protein,

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albumin, and uric acid will be measured. FSH, HIV screen, HBsAg and HCV antibody will only be measured at V1 for eligibility purposes.

6.5.4.2.1 Fasting Lipid profile

The following tests are included in the fasting lipid profile but are not limited to triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, VLDL cholesterol and non-HDL cholesterol. LDL cholesterol, VLDL cholesterol and non-HDL cholesterol will be calculated unless triglycerides > 400 mg/dL in which case only a direct LDL cholesterol assay will be employed.

6.5.4.3 Urinalysis

Dipstick measurements for specific gravity, protein, glucose and blood will be performed. WBC and RBC sediments will also be measured as a reflex if the dipstick is abnormal. Dipstick will be performed by the central lab. The urine albumin/creatinine ratio will also be measured to assess the presence of micro- or macroalbuminuria in patients with T2DM or pre-diabetes at baseline.

6.5.5 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed at baseline (Visit 2), yearly visits, and at the end of study visit. ECG's will be read by a central vendor. Each ECG tracing should be labeled with the study number, patient initials (if applicable), patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities should also be recorded on medical history/ adverse events eCRF page. Any potential endpoints should be recorded on the Clinical Study Endpoint Tracking Form eCRF.

6.5.6 Pregnancy and assessments of fertility

This study includes women of non-child bearing potential and therefore pregnancy test should be performed to detect unexpected pregnancies. A positive urine pregnancy test requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative. If the serum β-hCG is positive, the patient must be discontinued from study treatment but should continue follow up in the trial.

6.5.7 Appropriateness of safety measurements

Safety endpoints used in this trial are standard endpoints in demonstrating safety of investigational agents in clinical trials. Safety events of special interest in the following categories will be adjudicated by expert adjudication committee. Allergies/ Immunological events, serious infections and malignancies. Additionally, laboratory measurements will be canakinumab will be measured due to the hypothetical risk of immune response to the study treatment. These safety events of special interest represent hypothetical risks of canakinumab treatment.

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6.6 Other assessments

6.6.1 Assessment of durability of glycemic control for T2DM (exploratory endpoint)

These analyses are performed for patients with type 2 diabetes mellitus (T2DM) at randomization (defined in Section 4).

Patients with T2DM at randomization may be treated with any anti-diabetic medicine approved for use by local health authorities.

Long term glucose control durability of canakinumab will be assessed in patients with T2DM and HbA1c<7.0% at randomization by performing failure of glycemic control analysis. The first assessment of failure of glycemic control is at 6 month visit and thereafter every 6 months. Failure of glycemic control is defined as HbA1c $\geq$ 7.5% confirmed by a second HbA1c measurement within 6 weeks of the initial result. During this trial investigators should increase anti-diabetic medications or start new anti-diabetic medications only after HbA1c $\geq$ 7.5% has been confirmed.

6.6.2 Healthcare Resource Utilization

Healthcare Resource utilization data will not be collected in this study

6.6.3 Patient Reported Outcomes

Patient reported outcomes (PRO) have been identified as important in the post MI patient population. While a variety of relevant concepts within the context of canakinumab have been identified, the concepts of tiredness, physical function and performance function have been selected as prioritized measurement concepts. In order to measure these concepts a set of PRO instruments will be administered.

The PRO instruments to be included in this trial, where available, are the SF-36, the Multidimensional Fatigue Symptom Inventory – Short Form (MFSI-SF) and the EQ-5D. Details on each of these instruments are provided in addition to the target population.

For onsite visits only, it is strongly encouraged patients complete the questionnaire(s) before other clinical assessments.

Completed questionnaires will be reviewed and examined by the investigator before the clinical examination for responses which may indicate potential AEs or SAEs. The investigator should review not only the responses to the questions in the questionnaires but also any unsolicited comments written by the patient

If the occurrence of AEs or SAEs is confirmed, the physician must record the events as per instructions given in Section 7.1 of the protocol. Investigators should not encourage the patients to change the responses reported in the PRO questionnaires

Patient Reported Outcome Measures

Baseline Post MI

1. **SF-36**

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Target population: Patients who are post MI 30 days to less than 6 months in US and pre-defined EU countries.

The SF-36 has been selected to measure physical and performance function amongst patients post MI at several time points throughout the trial. The SF-36 is a 36 item measure developed by Cathy D. Sherbourne and John E. Ware. The SF-36 encompasses generic health concepts considered to be relevant across age groups, disease states and treatments types and has been validated in many disease states. For the purposes of this trial we will focus on the physical function and physical role domains, however the full instrument will be completed. The SF-36 will take patients approximately 5-10 minutes to complete. For this trial the acute version of this measure which includes a one week recall period will be utilized.

The SF-36 will be administered, where available, to patients enrolled in trial sites located in the U.S. and countries under the authority of the E.M.A. only. In addition, only patients who had a MI 30 days to less than 6 months of their enrollment date will be targeted for completing the SF-36. The SF-36 will be given to patients to complete in clinic as per the study assessment schedule.

2. **MFSI-SF**

Target population: Patients who are post MI 30 days to less than 6 months in US and pre-defined EU countries.

The MFSI-SF is a 30 item measure developed by Danette Hann, Paul B. Jacobsen, and Kevin D. Stein. The MFSI-SF encompasses a wide spectrum of concepts related to fatigue including physical, mental and emotional tiredness. This instrument has a 7 day recall period and is expected to take approximately 5 minutes for patients to complete. This instrument has been selected to measure tiredness in patients post MI and post stroke at several time points throughout the trial.

The MFSI-SF will be administered, where available, to post MI patients enrolled in trial sites located in the U.S. and countries regulated under the authority of the E.M.A. only. In addition, only patients who had a MI 30 days to less than 6 months of their enrollment date will be targeted. The MFSI-SF will be given to patients to complete in clinic as per the study assessment schedule

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3. **EQ-5D**

Target population: All patients enrolled in the trial

Generic multidimensional health-related quality of life will be assessed with the EuroQoL (EQ-5D). The EuroQol EQ-5D is a simple but effective standardized instrument designed for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides both a compact descriptive profile and a single index value that can be used in the clinical and economic evaluation of health care.

The EQ-5D measures five domains (mobility, self-care, usual activity, pain/discomfort & anxiety/depression).

There are two parts to this questionnaire. The first, 'health state classification' consists of five questions. The second, 'Visual Analogue Scale Thermometer' consists of a visual analogue scale. This generates a self-rating of current health-related quality of life. This will be used with the health state classification to build a composite picture of the respondent's health status.

- Data capture

EQ-5D enables an accurate self-description of current health-related quality of life to be easily recorded. Self-explanatory instructions to respondents are provided within the questionnaire and it takes about two minutes to complete.

- Health State Classification

The first page consists of five questions. The respondent is asked to indicate his/her current health state, by ticking the most appropriate of three statements about each of the five quality of life dimensions.

Each statement represents an increasing level of severity (1=no problem, 2=some or moderate problem, 3= unable or extreme problem). For example, a respondent with 'no problem' for each of the five questions will be said to have a health status of 11111.

- Visual Analogue Scale 'Thermometer'

The 'Thermometer' has end points of 100 (best imaginable health state) at the top and 0 (worst imaginable health status) at the bottom.

The respondent will rate his/her current health status by drawing a line from the box marked 'Your health status today' to the appropriate point on the 'thermometer' scale.

The site staff should record the two digit reading on the thermometer (where the line by the respondent crosses the thermometer) on the appropriate space in the CRF.

Missing or ambiguous values will be left blank.

Note: Questionnaire should be completed by the patient at the center, where available, before any other assessments take place.

6.6.4 Stroke Functional Assessment Sub-Study

Pre-clinical models indicate that anti-inflammatory therapy and specifically IL-1β blocking therapy may limit the size of stroke impact in brain tissue and facilitate functional recovery

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from stroke. Therefore, this clinical trial includes a sub-study on functional assessment of the patients recovering from stroke experienced during this trial and agreeing to participate in this sub-study in order to support the hypothesis that canakinumab therapy facilitates functional recovery from stroke.

The following 3 assessments will be performed on all patients who have suffered a stroke during the trial.

6.6.4.1 The Modified Rankin Scale

Performed 30 and 90 days post stroke: The effects of canakinumab on patients who undergo an ischemic stroke during the study and washout period will be assessed using the Modified Rankin scale (mRS), which provides an assessment of overall global neurologic function through serial observation of a patient's ability to perform Activities of Daily Living (ADL). A diagnosis of ischemic stroke will be determined by usual Standard of Care, and will include neurologic signs and symptoms of ischemia accompanied by radiologic studies which confirm the clinical diagnosis, as well as eliminating hemorrhagic stroke as a possible cause.

Patients will be examined at 30 and 90 days post-stroke by a Consulting Neurologist, who will score the serial examinations as noted below. Day 90 post-stroke assessment will be the primary outcome of this sub-study.

Grade Description

0 No symptoms at all

1 No significant disability despite symptoms: able to carry out all usual duties and activities

2 Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance

3 Moderate disability: requiring some help, but able to walk without assistance

4 Moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance

5 Severe disability: bedridden, incontinent, and requiring constant nursing care and attention

6 Death

6.6.4.2 MFSI-SF

Performed 30 and 90 days post stroke: Any patient who has a stroke at any time after enrollment in the trial will be targeted to complete the MFSI-SF instrument, where available, 30 days and at month 3 post their stroke event to assess tiredness. Any patient in the US or predetermined EU countries, who is to completing the MFSI-SF as a post MI patient and then has a stroke event (also recurrent stroke events) will also complete this questionnaire.

6.6.4.3 SIS-16

Performed 30 and 90 days post stroke: The SIS-16 has been selected to measure physical function and performance function in patients post stroke at several time points throughout the trial. The SIS-16 is a 16 item measure which was developed by Pamela W. Duncan. The SIS-

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16 encompasses a spectrum of concepts for physical function and performance function specific to stroke. The instrument utilizes a 2 week recall period.

The SIS-16 will be administered, where available, at all trial sites to any patient who has a stroke occur at any time after enrollment as well recurrent stroke events. The SIS-16 will be given to patients to complete in clinic at 30 and 90 days post their stroke event.

6.6.5 Pharmacokinetics

6.6.5.1 Blood collection

All blood samples must be taken at each indicated visit prior patient receiving their study medication injections. Blood samples will be taken at any time point by either direct venipuncture or an indwelling cannula inserted in a forearm vein.

For each scheduled PK sample, 2 mL of blood will be drawn into a plain barrier tube, to obtain 1.5 mL serum. The sample will be allowed to clot during 45 minutes at room temperature. The serum will be obtained by centrifugation at approximately 2500 g for 10 minutes. The sample will be split into **two** aliquots to be transferred into freezer-proof polypropylene screw-cap tubes. Serum tubes will be frozen within 90 min of venipuncture and kept at ≤ -18°C pending shipment on dry ice. One of the two serum samples is to be kept at the study site as a backup while the other one will be shipped to the central lab.

For a detailed description of blood sampling schema, please refer to the Blood Log in Appendix 2

Time points for collection:

- Baseline (Month 0): pre-dose
- Month 1.5 (pre-dose)
- Month 3 (pre-dose)
- Month 12 (pre-dose)
- Month 18 (pre-dose)
- Month 36 (pre-dose for all normoglycemic and Type 2 diabetes mellitus patients)
- Washout period (pre-dose)

6.6.5.2 Analytical method(s)

An ELISA method will be used for bioanalytical analysis of canakinumab in serum, with an anticipated lower limit of quantification (LLOQ) of 100 ng/ml. The detailed method description to assess canakinumab concentration will be described in the bioanalytical raw data of the study and in the respective Bioanalytical Data Report (BDR)

6.6.5.3 PK sample handling, labeling and shipment instructions

6.6.5.3.1 Sample labeling

The samples for the pharmacokinetic profile will be labeled as follows:

PK

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Study Code: CACZ885M2301

Patient Number:

Sample Number:

Date / Study Day:

Required Time:

Labels will be provided to the investigator.

For each shipment, the same procedure described in Section 6.6.6.3 PK sample handling, labeling and shipment instructions has to be followed.

6.6.6 Pharmacodynamics

Total IL-1β (sum of free and bound canakinumab) will be determined in serum.

Pharmacodynamic (PD) samples are to be collected at visits shown in Table 6-1.

6.6.6.1 Blood collection

All samples must be taken prior receiving their injections All blood samples will be taken, prior to dosing, by either direct venipuncture or an indwelling cannula inserted in a forearm vein.

For each scheduled PD sample, 3 mL of blood will be drawn into a plain barrier tube, to obtain 1.5 mL serum. The sample will be allowed to clot during 45 minutes at room temperature. The serum will be obtained by centrifugation at approximately 2500 g for 10 minutes. The sample will be split into two aliquots to be transferred into freezer-proof polypropylene screw-cap tubes. Serum tubes will be frozen within 90 min of venipuncture and kept at ≤ -18°C pending shipment on dry ice. One of the two serum samples is to be kept at the study site as a backup while the other one will be shipped to the central lab.

For a detailed description of blood sampling schema, please refer to the Blood Log in Appendix 2

Time points for collection:

- Baseline (Month 0): (pre-dose)
- Month 1.5(pre-dose)
- Month 3 (pre-dose)
- Month 12(pre-dose)
- Month 18 (pre-dose)
- End of study
- Wash-out period (pre-dose)

PD parameters: Total IL-1β in serum, this being the sum of free and bound canakinumab; rate of IL-1 production, clearance, and its binding affinity to canakinumab.

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6.6.6.2 Analytical method(s)

Total IL-1β will be analyzed in serum by means of a competitive ELISA assay, limit of detection (LOD) at 0.25 pg/ml.

Details of the analytical methods to assess total IL-1β in serum will be described in the bioanalytical data report.

6.6.6.3 PD sample handling, labeling and shipment instructions

6.6.6.3.1 Sample labeling

The samples for the pharmacodynamic profile will be labeled as follows:

PD

Study Code: CACZ885M2301

Patient Number:

Sample Number:

Date / Study Day:

Required Time:

Labels will be provided to the investigator.

For each shipment, the same procedure described in Section 6.6.6 PK sample handling, labeling and shipment instructions has to be followed.

6.6.7 Immunogenicity assessments

Anti- canakinumab antibodies concentrations will be assessed in serum.

Blood samples for Immunogenicity (IG) assessments are to be collected at visits shown in Table 6-1.

6.6.7.1 Blood collection

For each scheduled IG sample, 1 mL of blood will be drawn into a plain barrier tube, to obtain 500 µL serum. The blood sample will be allowed to clot during 45 minutes at room temperature. The serum will be obtained by centrifugation at approximately 2500 g for 10 minutes. Serum tubes will be frozen within 90 minutes of venipuncture and kept at ≤ -18°C pending shipment on dry ice.

If anaphylactoid reactions occur after injection, two more samples (at the time of the event and 8 weeks later) need to be taken.

6.6.7.2 Immunogenicity sample handling, labeling and shipment instructions

6.6.7.2.1 Sample labeling

The samples for the IG profile will be labeled as follows:

Anti- canakinumab Detection

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Study Code: CACZ885M2301

Patient Number:

Sample Number:

Date / Study Day:

Required Time:

Labels will be provided to the investigator.

For each shipment, the same procedure described in Section 6.6.6.3 PK sample handling, labeling and shipment instructions has to be followed.

6.6.7.3 Analytical method(s)

IG is analyzed by BIAcore. The system monitors the interaction between two molecules, of which one is attached to the sensor surface and the other if free in solution. In this assay canakinumab is reversibly bound to protein G, which is covalently bound to the specific sensor surface on which the serum samples are injected. Binding of potential anti-canakinumab antibodies is detected in real time as mass accumulation on the sensor surface. The detection is based on Surface Plasmon Resonance.

Details of the analytical methods to assess anti- canakinumab antibodies in serum will be described in the bioanalytical data report.

6.6.8 Pharmacogenetics/pharmacogenomics

The Study includes an optional pharmacogenetic component which requires a separate signature if the patient agrees to participate. It is required as part of this protocol that the Investigator presents these options to the patient. Should a patient choose not to participate in the pharmacogenetics sampling they may still continue into the trial.

Exploratory pharmacogenetics research studies are planned as a part of this study with the objectives of identifying inherited genetic factors which may (1) be related to major cardiovascular event, type 2 diabetes, hemostasis, inflammation, lipid, and/or coagulation disorders (2) predict response to treatment with canakinumab, or (3) predict genetic predisposition to side effects. We hope to develop a better understanding of major cardiovascular event and type 2 diabetes, and how patients respond to canakinumab.

Sample collection: One 10 mL blood sample will be collected at baseline (Visit 2) in an EDTA tube. After collection, the sample must be inverted several times to prevent clotting. If the blood draw at Visit 2 is missed, the sample should be taken at the next visit that a blood draw is already scheduled. Only one blood sample should be taken from the patient for this pharmacogenetic study. These samples will be shipped to the central lab. The sample will be shipped to the central lab then be transferred to the Data and Laboratory Coordinating Center for DNA extraction, pharmacogenetic analysis and storage.

Lab manuals will be provided with detailed information on sample collection, handling, and shipment. The sample collection date and exact time must be entered on the sample collection CRF (eCRF) page.

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Any DNA derived from the sample that remains after analysis may be stored for up to 15 years to address scientific questions related to canakinumab, major cardiovascular event or type 2 diabetes. Refer to Section 6.6.8 , Pharmacogenetics / pharmaocogenomics for the time schedule for pharmacogenetic blood sampling.

6.6.9 Other biomarkers

Biomarker measurements will be obtained on all patients at the visits indicated in the study assessment schedule. A panel of biomarkers may include but are not limited to:. IL-1Ra, IL-6, IL-18, leptin, adiponectin (total and high MW), TNFα, PAI-1 and fibrinogen .

An additional sample will be sent to the Data and Laboratory Coordinating Center for long term storage. Upon completion of the study these samples will be analyzed for cardiovascular and metabolic biomarkers and genetic analysis, if prior written informed consent is obtained

7 Safety monitoring

7.1 Adverse events

An adverse event is the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) occurring after signing informed consent.

Adverse events should be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria they induce clinical signs or symptoms, they are considered clinically significant or they require therapy.

The occurrence of adverse events should be sought by non-directive questioning of the patient during the screening process after signing informed consent and at each visit during the study

Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease

All adverse events, which are non protocol endpoints, must be recorded on the Adverse Events CRF with the following information:

1. the severity grade [mild, moderate, severe]
2. The relationship to the study treatment (Reasonable possibility that the AE is related: No, Yes)
3. Its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported at the time of the end of the study
4. whether it constitutes a serious adverse event (SAE)
5. the action taken regarding study treatment

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6. whether medication or therapies taken (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
7. the outcome (not recovered/not resolved; recovered/resolved; recovered/resolved with sequelae; fatal; or unknown)

An SAE is defined as any adverse events (appearance of or worsening of any pre-existing condition, undesirable sign(s), symptom(s) or medical condition, which are not protocol endpoints, that meet the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

Study-specific adaption of the standard definition of AEs and SAEs

In order to avoid double reporting and unblinding of study endpoints, a study specific exemption has been requested from the Health Authorities not to report study endpoints as serious adverse events/adverse events. Therefore, any cardiovascular event sent for adjudication as a potential study endpoint or is reported as non-adjudicated cardiovascular endpoint by the investigator will not be reported as an adverse event /serious adverse event but will be captured on the Clinical Endpoint Form eCRF. Only if adjudication committee determines that the event is not a study endpoint, will this event be reported as an adverse / serious adverse event following procedures described in Section 7.2 Serious adverse event reporting.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 7.2.

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); study drug dosage temporarily interrupted; study drug permanently discontinued; concomitant medication given; non-drug therapy given. The action taken to treat the adverse event should be recorded on the Adverse Event CRF.

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Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent. - Assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, suspected relationship to the study treatment, interventions required to treat it, and outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

The investigator should also instruct each patient to report any new Adverse Experiences (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonable be related to study treatment. This information should be recorded in the investigator's source documents, and if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse event reporting

To ensure patient safety, every SAE, regardless of suspected causality, except for those being adjudicated as endpoints or are reported as non-adjudicated cardiovascular endpoint by the investigator, which occur after the patient has provided informed consent and until 90 days after the last study visit (following the last administration of study treatment if there are post-treatment follow-up visits) must be reported to Novartis within 24 hours of learning of the occurrence. Any SAEs experienced after this 90 day period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug.

Information about all SAEs (either initial of follow-up information) may be collected and recorded on the electronic Serious Adverse Event Report Form that is part of the study eCRFs. If, for any reason, the SAE information (or follow-up information)can not be entered into the electronic SAE form within 24 hours of becoming aware of the SAE (or the follow-up information), the information must be recorded on the paper SAE Form and faxed to Novartis. The investigator must assess the relationship of any SAE to study drug(s), complete the eCRF or paper SAE Report Form in English.

When SAEs are recorded in the electronic SAE form, these data will automatically be submitted to Novartis after investigator signature or after 24 hours of entry, whichever occurs first

When the SAEs are recorded on paper SAE forms, these should be fax within 24 hours of awareness of the SAE to Novartis Clinical Trials Safety Operations in the UK at Fax Number 0044 1403 323500. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow- up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not and whether the patient continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a Drug Safety and

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Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

Reporting of events (including coincidental cardiovascular events) that are both study endpoints and AE's / SAE

The integrity of this study may be compromised if cardiovascular events that are study endpoints are systematically unblinded in order to fulfill European SUSAR reporting requirements for SAE (European Commission ENTR/CT3 Guideline (2006)). Therefore, in this study potential study endpoints are excluded from the definition of AE's and SAE's and are not to be captured as AE and SAE's but only on the relevant study endpoint CRF. These events are therefore NOT to be reported to Novartis within 24 hours on SAE forms and will not be reported to regulatory agencies, IRB's or investigators other than as a study endpoint in the Clinical Study Report.

The following endpoints are excluded from the definition of AEs and SAE's in this trial:

- Death
- Non-Fatal MI
- Stroke (e.g. hemorrhagic stroke, ischemic stroke)
- Unstable angina requiring unplanned coronary revascularization
- Stent Thrombosis (per ARC definition)
- Hospitalization or prolongation of hospitalization for heart failure
- Critical Limb ischemia
- Limb amputation
- Transient Ischemia Attack (TIA)
- New onset type 2 diabetes (NOD)
- Non-Coronary revascularization procedures
- Coronary angiography / Coronary Revascularization (PCI or CABG)
- Atrial fibrillation/ atrial flutter/ supraventricular tachycardia
- Pulmonary embolism and deep vein thrombosis

The Data Monitoring Committee (DMC) will review these endpoint data throughout the trial. Should the DMC make recommendations on the conduct of the trial that are considered to have significant bearing on the benefit risk of the trial, these will be communicated to competent authorities, IRBs/IECs and investigators and the ECs by Novartis in an appropriate timescale.

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Should an investigator report an event consistent with the events listed above as an SAE in addition to as an endpoint, Novartis will consider this an endpoint and will not unblind or report such an event to agencies or IRBs.

Any other endpoint that is not listed under the pre-specified endpoints above should be reported as SAE. If it meets SUSAR criteria, it will be unblinded; a report to competent authorities and relevant ethics committees and issuance of an IN will occur.

Events that following data review and adjudication are deemed not to be endpoints for this study will be reported as AEs and SAEs, as soon as adjudication process has been completed, following standard reporting guidelines.

It is important to note that ALL deaths must be reported as an endpoint and sent for adjudication. Only those that the adjudication committee deems not to be of CV cause will then be reported as an SAE. Study site staff will evaluate death events for SAE reporting after being notified that the adjudication committee deemed the death event not to be of CV cause.

7.3 Pregnancies

Women of child-bearing potential are excluded from this study; however, in the event a woman became pregnant we must ensure patient safety. Each pregnancy in a patient on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

7.4 Data Monitoring Committee

An external and independent DMC will be formed for this trial to periodically review safety information, and to evaluate the interim results relative to pre-defined statistical criteria to see if the trial has reached standards allowing stopping for proof of efficacy or for futility

The DMC will include experts in cardiovascular and cerebrovascular disease, T2DM, large scale clinical trials and statistics; the members will review the results confidentially and will have no other roles in the study.

The membership of the DMC and the responsibilities of the DMC and Novartis will be defined in a separate document entitled the “Data Monitoring Committee Charter.” The DMC Charter will include information about the data flow, purpose, timing of DMC meetings, guidance in the decision-making process, communication strategy, procedures for ensuring confidentiality, procedures to address conflicts of interest, and statistical monitoring guidelines.

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7.5 Adjudication Committees

There will be two separate adjudication committees for this study.

7.5.1 Cardiovascular clinical events adjudication committee

Cardiovascular clinical events will be adjudicated under blind by an adjudication committee, composed of reviewers who are experts on cardiovascular and cerebrovascular disease and T2DM. This measure is designed to ensure the objectivity, reliability and validity of the event classification. The procedures for reporting and case definitions are detailed in a separate charter document. The following primary and secondary cardiovascular endpoints will be adjudicated:

- All death
- Non fatal MI
- Stroke (e.g. hemorrhagic stroke, ischemic stroke)
- Unstable angina requiring unplanned coronary revascularization
- New onset type 2 diabetes mellitus

Definitions of clinical endpoints are described in Appendix 3.

The primary endpoint will be assessed based on MACE adjudicated to have occurred between a patient's randomization and either

1. the patient's entry into the wash-out period,
2. or the patient's entry into the long-term safety extension study,
3. or for those patients not proceeding to neither wash-out period or safety extension the patient's end of study visit, but only if it occurred during the close-out period,
4. or otherwise the end of the close-out period (analysis cut-off).

Thus, events occurring after informed consent but before randomization do not need to be adjudicated and should instead be reported as adverse or serious adverse events. Events occurring in the safety extension study should be reported as specified in the clinical trial protocol for the safety extension study.

Baseline and yearly ECG will be obtained to assess interval ECG changes for study patients. Myocardial infarctions detected as interval ECG changes without clinical sequelae ("silent myocardial infarction") will be reported as endpoint. Interpretation of all scheduled ECGs will be done by a central ECG vendor (eRT, Philadelphia, PA) using qualified expert physicians.

The diagnosis New MI should be used when an ECG shows an MI that was not present on previous ECGs for the study patient. Previous ECGs must be available. This diagnosis should be used the first time the new MI is seen, but not for subsequent ECGs.

7.5.2 Allergy, serious infections and malignancies Adjudication Committee (AIM)

New allergy, serious infections and malignancies (whether newly detected or worsening of an existing non-basal cell malignancy) will be adjudicated by a separate expert committee composed of experts in allergy/immunology, infectious diseases, and oncology. This measure

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is designed to ensure the objectivity, reliability and validity of the event classification. The procedures for reporting and case definitions are detailed in a separate charter document.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis or study team representative will review the protocol and (e)CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the (e)CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on (e)CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the (e)CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the (e)CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the OC/RDC system. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data (either paper or CD-ROM) for archiving at the investigational site.

8.3 Database management and quality control

Novartis staff review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the

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electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff who will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

ECG readings will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study drug dispensed to the patient will be tracked using an Interactive Voice Response System (IVRS/IWRS). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

The occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete for the main study (i.e. excluding the washout period and long-term open-label safety follow-up extension study, which will be reported separately) and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the Clinical Science Unit Head and the IIS Program Head.

Each occurrence of a code break via IVRS/IWRS will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Pharmacogenetic samples:

To maximize confidentiality, all samples and the information associated with the samples will be double-coded to prevent the exposure of the patient's information and identity. This double-coding process allows Data and Laboratory Coordinating Center to go back and destroy the sample at the patient's request. In addition, sample information is stored in one secured database while genetic data is stored in an independent secured database.

The use of pharmacogenetics to search for biomarkers of disease and drug action is exploratory. Any results from this pharmacogenetic study will not be placed in the patient's medical records.

9 Data analysis

9.1 Analysis sets

The following analysis populations will be defined for statistical analysis:

- **Screened set** – All patients who signed the informed consent.

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- **Randomized set** – All patients who received a randomization number, regardless of receiving trial medication.
- **Safety set (SAF)** – All patients who received at least one dose of study treatment and have at least one post-baseline safety assessment. Of note, the statement that a patient had no AEs also constitutes a safety assessment. Patients will be analyzed according to treatment received. Treatment received will be considered to be canakinumab 150 mg for the whole duration of the trial for patients that received at least one canakinumab 150 mg injection at any point during the trial, canakinumab 50 mg for the whole duration of the trial for patients that received at least one canakinumab 50 mg injection and no canakinumab 150 mg injection at any point during the trial, and placebo for the whole duration of the trial for patients that received at least one placebo injection and no injection of either canakinumab dose at any point during the trial.
- **Full analysis set (FAS)** – All randomized patients. This is the primary efficacy population applied in all efficacy endpoints. Following the intent-to-treat principle, patients are analyzed according to the treatment they have been assigned to at the randomization. However, patients who have not been qualified for randomization and who have been inadvertently randomized into the study are excluded from FAS, provided these patients have not received study treatment.
- **Per protocol set (PPS)** – a subset of the FAS, consists of all randomized patients in FAS who take at least one dose of study medication and have no major protocol deviations affecting the primary endpoint analyses. Major protocol deviations leading to exclusion from PPS will be specified prior to database lock on a blinded basis and documented in a separate document.

Note: The last part of the definition of the FAS is what is often referred to as misrandomized patients; i.e. patients for whom IVRS calls were made by the site either prematurely or inappropriately prior to confirmation of the patient's final randomization eligibility and double-blind medication was not administered to the patient. These patients would subsequently not continue to take part in the study or be followed-up. Misrandomized patients will not be included in the FAS, but they will be included in the Randomized Set. Further exclusions from the FAS may only be justified in exceptional circumstances.

9.2 Patient demographics and other baseline characteristics

The number of patients screened, randomized and included in FAS will be presented by treatment group and overall for the screened set. In addition, the reasons of screen failures will be provided for screened set as well. The number and percentage of patients in the randomized set who completed the study, who discontinued the study and the reason for discontinuation will be presented for each treatment group and all patients. The frequency (%) of patients with major protocol deviations as well as the criteria leading to analysis sets will be presented in separate tables for the randomized set. Finally, the number of enrolled and randomized patients by region as well as the number of patients enrolled and randomized per region and country will be presented descriptively for the randomized set.

Baseline value is defined as the last non-missing assessment prior to the first dose of randomized study medication unless specified otherwise.

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The following common background and demographic variables will be summarized using descriptive summary statistics (for continuous variables mean, median, standard deviation, Q1 (25th percentile), Q3 (75th percentile), minimum and maximum and for categorical variables frequency and percentage):

- Age [years]
- Sex
- Race
- Ethnicity
- Height [cm]
- Weight [kg]
- Body mass index [kg/m^2] calculated as weight [kg]/ $height^2$ [m^2]
- Waist circumference [cm]
- Sitting pulse [bpm]
- Mean sitting SBP [mmHg]
- Mean sitting DBP [mmHg]
- Smoking history
- Alcohol history
- Region (Country) of enrollment
- Cardiovascular risk factors and other co-morbidities including but not limited to following:
    - Diabetes mellitus, complications of diabetes
    - Hypertension
    - Dyslipidemia/Hyperlipidemia
    - Atrial fibrillation
    - Supraventricular tachycardia
    - Deep Vein Thrombosis
    - Pulmonary embolism
    - Prior repeated MI (multiple MIs in medical history)
    - Prior PCI
    - Prior stent implantation (incl. drug eluding stent or bare metal stent)
    - Prior CABG
    - Prior TIA/stroke
    - Congestive heart failure
- Medical history of gout
- Post MI index group
- hsCRP [mg/L (two values available with the mean of these two used in analysis)]
- HbA1c [%]

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- FPG [mmol/L]
- Lipid profile
- Glycemic status: T2DM, pre-diabetes, normoglycemic
- Level of exercise
- Family history of MI, stroke or diabetes
- Highest degree of education

Treatment group comparability will be examined using the Cochran-Mantel-Haenszel test for the categorical variables and the F-test for the continuous variables as appropriate. These p-values will be provided for descriptive purposes and will not be considered to define any formal basis for determining factors that should be included in statistical models. If imbalances between treatment groups with respect to some variables occur, additional supplemental analyses may be performed to assess the impact of these imbalances as appropriate.

9.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

Study drug

The duration of the double-blind treatment will be computed as the time from the first injection to the first out of

1. the last injection date plus a quarter year (91 days),
2. the patient's death
3. or the patient's study completion visit during the study close-out period.

This algorithm reflects the planned treatment schedule and the long half-life of the study drug. The duration of the treatment period will be summarized for the full analysis set and safety set by treatment group descriptively including by duration categories. The overall patient-years of treatment will be computed as the sum of patient years of double-blind treatment for all patients.

Duration of exposure to study treatment excluding interruptions will be computed and summarized as above, but not counting periods during which the last injection was more than a quarter year ago.

Prior and concomitant therapies

Prior or concomitant medications will be summarized for the safety set in separate tabulations based on the coding dictionary used. Medications will be presented in alphabetical order, by preferred terms and grouped by anatomical main group. Tables will show the overall number and percent of patients receiving at least one drug of a particular preferred term and at least one drug in a particular anatomical main group.

Prior medications and significant non-drug therapies are defined as any medications and significant non-drug therapies taken prior to the randomization visit. Concomitant medications and significant non-drug therapies are defined as those used during the double-

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blind period. Concomitant medications that were prohibited as per protocol and given during the conduct of the study as well as significant non-drug therapies will be summarized.

Furthermore, the following classes of medications to be precisely defined in the statistical analysis plan, at time of randomization and during the double-blind period, which are relevant to program indication, will be summarized separately:

- Anti-ischemic agents
  - Beta blockers
  - Intravenous or oral nitrates
  - Calcium channel blockers
- Anti-platelet agents
  - Acetylsalicylic acid (aspirin)
  - Non-aspirin oral anti-platelet agents (like P2Y12 inhibitors clopidogrel and prasugrel)
- ACE inhibitors (like ramipril)
- ARBs
- Lipid-lowering agents
  - Statins
  - Non-statins (like fibrates, binding resins and nicotinic acid)
- Diuretics
  - Thiazide diuretics
- Anti-diabetic medications
  - Insulin
  - Thiazolidinediones
  - Other oral hypoglycemic agents
- Proton pump inhibitors
- Anticoagulants

9.4 Analysis of the primary variable(s)

The primary analysis and all analyses of secondary/exploratory endpoints will use the Full Analysis Set (FAS), which reflects the intention-to-treat principle.

Unless otherwise specified all time-to-event analyses will be based on events occurring during the double-blind treatment period. This means that only events between a patient's randomization and either

1. the patient's entry into the wash-out period,
2. or the patient's entry into the long-term safety extension study,
3. or for those patients not proceeding to neither wash-out period or safety extension the patient's end of study visit, but only if it occurred during the close-out period,
4. or otherwise the end of the close-out period (analysis cut-off)

will be counted in these analyses.

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9.4.1 Variable

The primary efficacy variable is the time to first occurrence of a major adverse cardiovascular event (MACE), which is a composite endpoint consisting of cardiovascular death, non-fatal MI, and stroke. An independent adjudication committee will review and adjudicate all clinical events that constitute the composite of the primary endpoints on a blinded basis.

The time-to-event is computed as the number of days from randomization to the onset of the primary endpoint event. Data on patients who do not reach the primary endpoint by the study end date will be censored at the latest date they are known to be at risk.

9.4.2 Statistical model, hypothesis, and method of analysis

The primary statistical null hypotheses are

- H_{11}: The hazard rate of first adjudication committee confirmed MACE in the canakinumab 50 mg dose group is greater than or equal to the hazard rate of the placebo group
- H_{21}: The hazard rate of first adjudication committee confirmed MACE in the canakinumab 150 mg dose group is greater than or equal to the hazard rate of the placebo group.

Each null hypothesis is tested against the one-sided alternative that the hazard rate is smaller for the respective active dose group than for the placebo group.

These hypotheses will be tested by comparing each dose to placebo with a log-rank test stratified by time since index MI (30 days to < 6 months and ≥ 6 months) using Peto's exact method (Peto 1972) for handling ties on the full analysis set (FAS) according to the intent-to-treat principle. The family-wise error rate will be controlled at the two interim analyses and the final analysis using the closed testing procedure shown in Figure 9-1 using the graphical method of (Bretz, et al 2009); however, intersection null hypotheses involving the primary null hypotheses for both doses will be tested using Dunnett's test (Dunnett 1955). Specifically this means that for any intersection hypothesis from the full closure that contains both H_{11} and H_{21}, a Dunnett test for H_{11} and H_{21} is performed at the full significance level for the respective analysis (at the final analysis 2.45%), while all other hypotheses in that intersection receive zero weight. All other intersection hypotheses are tested with a weighted Bonferroni test. Protection of the family–wise error rate at level alpha is still guaranteed when the transition weights on the directed edges are chosen as in Figure 9-1 (see comment below) and all the tests on secondary variables are performed at the level resulting from the graphical procedure. The consonance of the test procedure (Brannath and Bretz 2010) has also been ensured as described below.

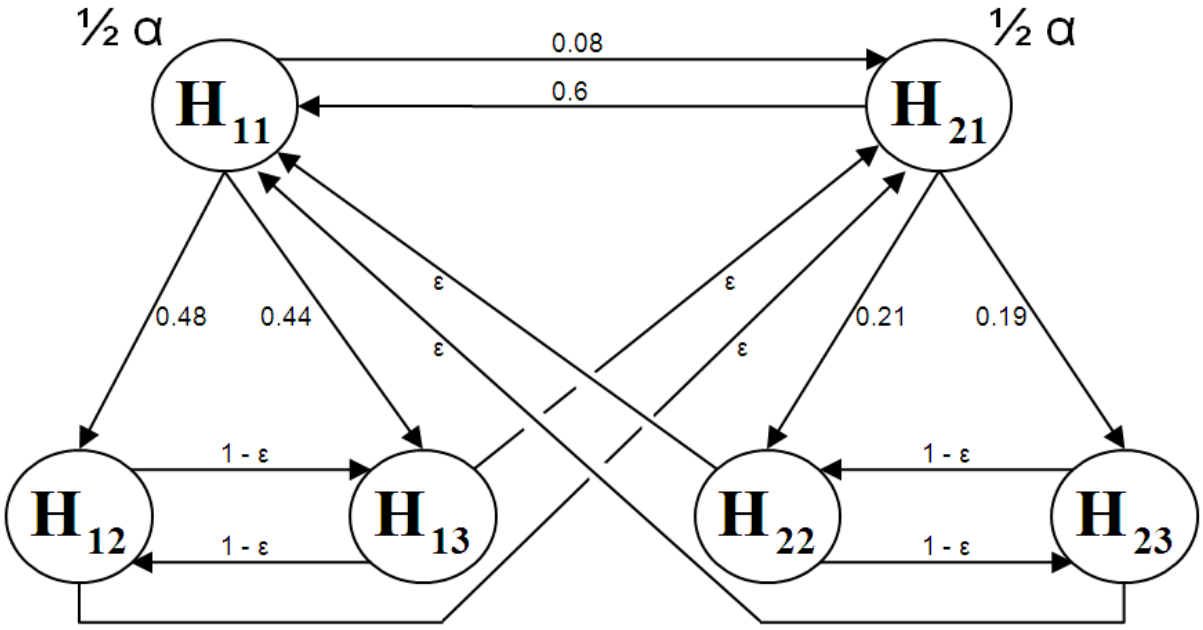
The testing procedure in Figure 9-1 initially assigns the entire available significance level (at the final analysis 2.45%) equally to the two primary null hypotheses relating to the two doses (at the final analysis 1.225% for each). Key secondary endpoints for a dose are only tested after successful rejection of the primary null hypothesis for that dose. In that case a slightly higher fraction of the local significance level is passed to the secondary CV composite endpoint than to the new onset of diabetes endpoint.

Note that if the primary endpoint for the 150 mg dose (null hypothesis H_{21}) is rejected 60% of the local significance level assigned to that null hypothesis is shifted to the primary endpoint for the 50 mg dose (null hypothesis H_{11}). In contrast after rejecting H_{11} only 8% of the local significance level assigned to H_{11} would be shifted to H_{21}. This reflects the possibility that the

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50 mg dose could potentially have the better safety profile of the two doses; hence, it would be desirable to demonstrate the efficacy of the 50 mg dose even after demonstrating the efficacy of the 150 mg dose. After the rejection of H_{11} 8% of the local significance level assigned to H_{11} is shifted to H_{21} in order to preserve the consonance of the test procedure; i.e. to avoid a situation in which the primary null hypothesis for the 150 mg would be rejected by Dunnett's test, but could not be rejected by the chosen closed testing procedure due to insufficient alpha being assigned to some intersection null hypotheses.

Figure 9-1 Closed testing procedure for primary and key secondary endpoints



H_{12} is the null hypothesis relating to the secondary CV endpoint for the 50 mg dose, H_{22} is the respective null hypothesis for the 150 mg dose. H_{13} is the null hypothesis relating to the new onset of diabetes endpoint for the 50 mg dose, H_{23} is the respective null hypothesis for the 150 mg dose. In the notation of Bretz, Maurer, Brannath and Posch, a weight of ε for an edge indicates an infinitesimally small weight. If a hypothesis (vertex) with such an outgoing edge is rejected and the vertex removed, no significance level is passed on along such an edge as long as there are other outgoing edges with positive weights. If after removal of another vertex only infinitesimal outgoing edges remain, then the algorithm of Bretz et al. turns them into edges with positive weights that sum to 1. In this specific procedure, this implies that no significance level is passed from the secondary null hypotheses of a dose to the primary null hypothesis of the other dose until both key secondary null hypotheses have been rejected. To ensure the sum of weights on all outgoing edges of a vertex is 1 when such edges are present, some edges are given a weight of 1 – ε. For any intersection hypothesis from the full closure that contains both H_{11} and H_{21}, a Dunnett test for H_{11} and H_{21} is performed at the full significance level for the respective analysis (at the final analysis 2.45%).

Two efficacy interim analyses, at which the trial could be stopped for demonstrated efficacy or one or both active arms could be stopped for futility will be performed respectively after 50% and 75% of the target number of 694 patients have experienced a primary endpoint. Futility criteria and the criteria other than purely formal statistical significance required for stopping the trial for demonstrated efficacy will be specified in the Data Monitoring Committee charter.

A fixed Bonferroni split of the one sided significance level will be used to account for the two efficacy interim analyses and the final analysis, with a significance level of 0.01% for the first

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and 0.04% for the second efficacy interim analysis. I.e. the closed testing procedure will be performed with an one-sided significance level of 0.01% at the first efficacy interim analysis, with an one-sided significance level of 0.04% at the second efficacy interim analysis and with an one-sided significance level of 2.45% at the final analysis. In this fashion the familywise type I error rate will be controlled at the overall (one-sided) significance level $\alpha = 2.5\%$.

The hazard ratios and their associated confidence intervals will be estimated by means of a (Cox 1972) proportional-hazards model stratified by time since index MI (< 6 months, ≥ 6 months) using treatment (canakinumab doses and placebo) as a factor in the model using (Peto 1972) exact method for handling ties. Kaplan-Meier plots will be presented to summarize the time to first event in the composite endpoint, by presenting the time-dependent cumulative frequency and percentage of patients who reach the primary composite endpoint by treatment group.

Should one of the two active arms be stopped due to safety reasons or futility, then thereafter the pre-specified testing procedure will be performed for the other arm treating all null hypotheses for the stopped arm as non-rejected. In such a case where one active arm is stopped, then additionally the target number of patients with a MACE that is still to be collected has to be adjusted. It will be reduced by 30%. The size of this reduction is based on the proportion of events assumed to be available for the non-stopped comparison during sample size calculations. Under the main scenario for sample size calculation, both active arms have a 23.9% relative hazard reduction; in that case the expected proportion of events for the comparison of one active arm versus placebo is $(1+0.761)/(1+0.761+0.761) \approx 0.7$ and 30% of events would be expected to occur on the other active arm. While it is not clear, whether there is any adjustment rule for determining the target number of patients with an event after stopping one trial arm that can be absolutely guaranteed to have no effect on the type I error rate, it is expected that the conservativeness of the testing strategy in this case will outweigh any such small effects.

9.4.3 Handling of missing values/censoring/discontinuations

Regarding time-to-event endpoints only observed events will be used in the analysis and in the primary analysis censoring of non-observed events will be assumed to be non-informative. Sensitivity analyses with respect to this assumption will be performed. Incomplete dates of events and censoring dates will be imputed as described below.

In the primary analysis, all patients, including those who discontinue study therapy due to lack of efficacy, adverse events or abnormal laboratory values will be followed until death or the end of the study. Information of patients discontinuing study drug or participation in trial visits will be collected whenever possible and will be used in the analysis. In patients who could not be followed up for primary outcome events, it is aimed to at least determine the vital status of the patients at the final visit.

The following rules will be applied separately for the composite MACE endpoint and for all its individual components. Patients who have not experienced the respective endpoint will be censored on the date of the last follow-up in the following way:

- for patients who die, the censoring date will be the date of death unless the patient withdrew his consent for the collection of follow-up information,

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- for patients who attend a final visit during close out, the censoring date will be the final visit date,
- otherwise the censoring date will be based on the last visit at which the investigator reported that it was known whether the patient experienced any clinical events since the last visit (i.e. answer of "yes" or "no" to this question, not "unknown". The last known date the patient was alive reported at that visit will be used, if the last known date the patient was alive is missing the day halfway between the date of the visit at which the patient was reported as alive on an unknown date and the last preceding visit at which the patient was known to be alive will be used.

Should the censoring date lie after the chosen analysis cut-off date, it will be set to the analysis cut-off date.

If the date of a MACE endpoint or of censoring is not known or is incomplete following all attempts to get an approximate date, a day will be imputed using the following algorithm:

- If only the month of the event is known, then the 15th day of this month will be imputed.
- If only the year of the event is known, then the 1st July will be imputed.
- If year, month and day are unknown, the randomization date will be imputed.
- If this imputation rule leads to a date before the randomization date or after a patient's last study visit or after a patient's death, but before the imputation the date could have been on one of these dates, then the date will be imputed as that date.

9.4.4 Supportive analyses

The components of the composite primary efficacy endpoint (CV death, fatal or non-fatal MI, fatal or stroke) will also be analyzed individually in order to evaluate their contributions to the overall treatment effect.

The primary endpoint will also be analyzed on the PPS. Additionally in an on-treatment analysis on the FAS patients will be considered censored at the latest one quarter year + 28 days (119 days) after the last study injection. Besides adjudicated endpoints investigator reported outcomes will also be analyzed.

Furthermore, pre-specified subgroup analyses will include age, sex, race, ethnicity, BMI, region, glycemic status, smoking status, baseline hsCRP level, LDL-C levels, SBP/DBP levels, statin, aspirin, gout and renal failure. Possible interactions between treatment and baseline variables will be evaluated with appropriate methods. Results will be presented graphically as forest plots. The objective of the subgroup analyses is to show the consistency of treatment effects across a wide variety of patient groups. Additional subgroup analyses will be considered and pre-specified prior to unblinding of trial database for final analysis. Additionally, the post-baseline subgroups of response in hsCRP response and target hsCRP levels achieved will be explored.

9.5 Analysis of key secondary and exploratory variables

Unless otherwise specified all time-to-event analyses will be based on events occurring during the double-blind treatment period (see Section 9.4).

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9.5.1 Secondary variables

Key secondary efficacy variables

The following key secondary variables will be used in the analyses:

- Time to the first occurrence of an adjudication committee confirmed composite cardiovascular endpoint consisting of the components of the primary endpoint and hospitalization for unstable angina requiring unplanned revascularization
- Time to adjudication committee confirmed new onset of type 2 diabetes among those with pre-diabetes at randomization

The following hypotheses will be tested with respect to the key secondary variables for the canakinumab 50 mg dose versus placebo

- H_{12}: The hazard rate of first adjudication committee confirmed secondary composite CV endpoint in the canakinumab 50 mg dose group is greater than or equal to the hazard rate of the placebo group
- H_{13}: The hazard rate of new onset of diabetes for pre-diabetic patients in the canakinumab 50 mg dose group is greater than or equal to the hazard rate of the placebo group

Each null hypothesis is tested against the one-sided alternative that the hazard rate is smaller for the canakinumab 50 mg dose group than in the placebo group. The corresponding hypotheses for the comparison of the canakinumab 150 mg dose versus placebo are H_{22} for the secondary composite CV endpoint and H_{23} for the new onset of diabetes endpoint.

All key secondary efficacy variables will be analyzed on the FAS with a log-rank test stratified by time since index MI. The hazard ratios will be estimated using a Cox regression model stratified by time since index MI. Kaplan-Meier plots showing each treatment will be provided. The multiplicity adjustment used to protect the familywise type I error rate is shown in Figure 9-1.

The secondary efficacy variable corresponding to new onset diabetes in patients with pre-diabetes at randomization will be the time from randomization to the first of repeated FPG > 126 mg/dL or the first of repeated HbA1c ≥ 6.5% or start of new anti-diabetic concomitant medication(s) for glucose lowering purpose. Due to the discrete nature of the time points when new onset of type 2 diabetes can be determined, events identified at the same visit time point for different patients will be considered as tied events and (Peto 1972)exact method for handling ties will be used. This assumes that for each of these patients new onset of diabetes occurred at some time point since the previous visit, but that due to the impossibility of continuous monitoring of the patients the true order in which each of them progressed to diabetes is unknown (Allison 1995). For this endpoint patients without new onset of diabetes will be considered censored at the time of their last laboratory assessment.

Other secondary efficacy variables

Although all-cause mortality is considered a very important secondary endpoint due to its importance as both an efficacy and safety outcome, it is not part of the pre-specified testing procedure for primary and key secondary endpoints, because given the expected number of

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deaths in the trial it would not have been possible to adequately power the key secondary mortality endpoint.

All-cause death and the composite of all-cause death, stroke or MI will be analyzed on the FAS with a log-rank test stratified by time since index MI. The hazard ratios will be estimated using a Cox regression model stratified by time since index MI. Kaplan-Meier plots showing each treatment will be provided. Patients who did not die will be considered censored at the last time they were reported to be alive.

Analysis of the washout period

Data from the double-blind treatment period and the washout period will be combined to assess to what extent canakinumab truly delayed progression to diabetes and to what extent it only masked diabetes during the double-blind treatment period. The analysis will take into account that masking of diabetes may have occurred in patients not diagnosed as diabetic during the core study that did not enter the washout period. A number of sensitivity analyses with a range of assumptions about these patients will be performed. These analyses will be specified in a detailed Statistical Analysis Plan prior to the first efficacy interim analysis.

Analysis of the Post-Stroke Functional Assessment Sub-Study

In line with the primary objective of the post-stroke functional assessment sub-study to evaluate canakinumab arms facilitates functional recovery from stroke, the primary endpoint for this sub-study is the modified Rankin scale assessment 90 days post-stroke. Further endpoints are the 30 day results of the modified Rankin scale assessment, the 30 and 90 day MFSI-SF and the 30 and 90 day SIS-16.

Analyses will be fully specified in a detailed Statistical Analysis Plan and will take into account that while patients were initially randomly assigned to treatments the subset of patients experiencing a stroke may represent a biased subset. The impact of the occurrence of fatal strokes in the main study on the results of the sub-study will also be considered.

9.5.2 Exploratory Efficacy variables

Exploratory time-to-event outcomes will be analyzed using Cox models including treatment with time since index MI as a stratification variable, along with Kaplan-Meier analyses. Exploratory continuous outcome variables (i.e. change from baseline of HbA1c, biomarkers, etc.) will be analyzed using both a repeated measures analysis of covariance adjusted for baseline value and time since index MI as a factor, as well as a descriptive analysis.

The following endpoints will be analyzed

- Time to other cardiovascular disorders with a known inflammatory component:
    - Time to first deep vein thrombosis/pulmonary embolism
    - Time to first supraventricular tachycardia/atrial fibrillation
    - Time to first stent thrombosis (probable or definite)
    - Time to first hospitalization or prolongation of hospitalization for heart failure
    - Time to first event of major coronary events composite (CHD death or MI)

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  - Time to first event of total vascular events composite consisting of primary endpoint, hospitalization for unstable angina, or for any other non-coronary ischemic event (transient ischemic attack or limb ischemia), any revascularization procedure (coronary and non-coronary) and limb amputation
  - Time to first event of coronary revascularization procedures (PCI or CABG)
  - Time to first event of stroke by etiology
- Time to nephropathy as assessed by urine albumin/creatinine ratio (≥ 30 mg/mmol) in patients with T2DM or pre-diabetes at baseline
- Glycemic control among those with type 2 diabetes at baseline defined by HbA1c and/or FPG or medical history and/or concomitant medications criteria in Section 4 (analyses will use baseline HbA1c, and baseline BMI as continuous covariates and the use of diabetic medications at baseline (yes/no) as a factor in the analysis models).
  - Time to failure of glycemic control defined as HbA1c ≥ 7.5% confirmed by a second HbA1c within 6 weeks in those patients that were diabetic at baseline with a baseline HbA1c < 7.0%
  - Change from baseline in HbA1c overall and by visit in all patients that were diabetic at baseline
- Change from baseline in biomarkers of cardiovascular and diabetes risk, including inflammatory biomarkers, glycemic control markers, β-cell function markers, FPG, HbA1c, and HOMA including
  - Achieved reductions from baseline in hsCRP
  - Target hsCRP levels achieved

9.5.3 Safety variables

Safety will be evaluated based on the safety set (SAF). The assessment of safety will be based primarily on the assessment of potential and identified risks defined in the safety profiling plan (SPP), the frequency of adverse events, laboratory abnormalities, and serious adverse events suspected by the investigators to be related to study treatments. Other safety data (like vital signs, ECG) will be summarized as appropriate.

Adverse events between informed consent and randomization

Adverse events between informed consent and randomization will be summarized by primary system organ class and preferred term. This summary will include events that would qualify as trial endpoints if they occurred after randomization, but which are to be reported as AEs prior to randomization.

Treatment emergent adverse events (AEs) excluding trial endpoints

The incidence of treatment emergent AEs (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) excluding trial endpoints will be summarized by primary system organ class (SOC), preferred term and also by severity and relationship to study treatment. If warranted, time to event analysis methods will be used. Standardized MedDRA Queries

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(SMQs) will also be employed. The MedDRA version used for reporting the study will be clearly identified.

If a patient reported more than one AE with the same preferred term, the AE with the greatest severity will be presented. If a patient reported more than one AE within the same primary system organ class, the patient will be counted only once with the greatest severity at the system organ class level, where applicable.

The number and percentage of patients reporting any AE during the double-blind period of the study will be summarized by primary system organ class, preferred term and treatment and also by SMQ and treatment.

Separate summaries will be provided for study drug related AEs, deaths, SAEs and, other significant AEs leading to discontinuation.

AEs of special interest

Frequencies of adjudicated immunological AEs (serious allergies/immunological events (e.g. immunological laboratory screen and anti-canakinumab antibodies), serious infections, and malignancies, whether newly detected or worsening of existing malignancies) will be reported.

Laboratory data

The summary of laboratory evaluations will be presented for three groups of laboratory tests (Hematology, Serum chemistry and Urinalysis).

Descriptive summary statistics for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by laboratory test and treatment group. Change from baseline will only be summarized for patients with both baseline and post baseline values.

In addition, shift tables by treatment group will be provided for all parameters (except for creatinine clearance, which will be calculated using the MDRD formula) in order to compare a patient's baseline laboratory evaluation relative to all post-baseline values.

The frequency and percentage of patients with clinically notable laboratory results after baseline will be tabulated.

Liver safety

The following analyses will be performed:

- The liver-related events meeting specified criteria standard table will be used to provide the number and percentage of patients having aspartate transaminase (AST), alanine transaminase (ALT) > 3, 5, 8, 10 x ULN or total bilirubin (TBL) >1.5, 2 x ULN or alkaline phosphatase (AP) > 2, 3 x ULN. The number and percentage of potential Hy's Law cases will be presented by treatment group. Potential Hy's Law cases are defined as those patients with AST or ALT >3xULN and TBL >2xULN and AP <2xULN at the same lab measurement.

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- A cross-tabulation of baseline and worst post-baseline values by below, within and above normal range categories will be provided. Shift tables will be provided for the parameters AST, ALT, TBL and AP. These summaries will be presented by laboratory test and treatment group.
- Standard laboratory tables will be produced as for all other laboratory parameters.
- The narrow and broad "Possible drug related hepatic disorders – comprehensive search" SMQ and the corresponding lower level SMQs will be presented including the respective preferred term frequencies covered under the SMQs.
- The overall SMQ/preferred term table will be used to provide the number and percentage of patients with hepatic disorders.
- eDISH plots will be provided representing the entire study population.
- Narratives for any patients discontinued due to liver function abnormalities will be prepared.

Vital signs

Descriptive summary statistics of vital sign variables for the change from baseline to each post baseline visit will be presented. These descriptive summaries will be presented by vital sign and treatment group. Change from baseline will only be summarized for patients with both baseline and post-baseline values.

ECG

Based on a standard 12-lead ECG, any new or worsening clinically relevant findings will be recorded as AEs except for ECG changes constituting study endpoints. Therefore, no separate presentation of ECG findings is foreseen

9.5.4 Resource utilization

Analyses of healthcare resource utilization data will be specified separately.

9.5.5 Patient Reported Outcomes

Exploratory efficacy patient reported outcome variables including those related to tiredness, physical function, performance function and health status, will be generated from the Modified Rankin Scale, MGSI-SF, SF-36, SIS-16, EQ-5D, Heath State Classification, and Visual Analogue Scale. These will be analyzed using a repeated measures analysis of covariance with baseline levels as a covariate and summarized descriptively.

EQ-5D

Health state classification will be converted to a score (during data analysis stage) according to a list provided. This list has 243 values for all possible EuroQoL health status. For example a health state of 11111 will have a score of 1.00 and a health status of 12132 will have a score of 0.09.

The analysis will involve the estimation of weighted indices over time for patients in each treatment group. The weighted indices will be displayed graphically along with the respective

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treatment means. The change from baseline in VAS scores will also be summarized using descriptive statistics.

Analysis based on EQ-5D data will be reported separately, and will not be part of the clinical study report.

9.5.6 Pharmacokinetics

A mixed effects modeling approach may be used to characterize the PK of canakinumab and it's binding to IL-1β. The relationship between population parameters such as CL/F and covariates such as dose, age, and weight may be investigated using graphical methods and simple regression models. Quality of individual fits to the dataset will be assessed, and individual model parameters (post-hoc estimates) may be obtained for each patient. Alternatively, in case the population based modeling may not be feasible, the analysis will be limited to the methodology based on predictive check, where the measures of systemic drug exposure (pre-dose trough levels) and biomarker response (IL-1 β) will be plotted against the data collected in previous trials.

9.5.7 Pharmacogenetics/pharmacogenomics

The exploratory pharmacogenetic studies are designed to investigate the association between genetic factors (genotypes) and clinical assessments (phenotypes) which are collected during the clinical trial. Without prior evidence of a strong association, a number of possible associations are evaluated with exploratory analyses. A range of statistical tests (chi-square tests, ANCOVAs, linear and logistic regression) are used for the analyses. Additional data, from subsequent clinical trials, are often needed to confirm associations. Alternatively, if the numbers of patients enrolled in the study are too small to complete proper statistical analyses, these data may be combined, as appropriate, with those from other studies to enlarge the data set for analysis.

9.5.8 Biomarkers

Biomarkers associated with cardiovascular disease will be measured. These include IL-1ra, IL-6, IL-18, leptin, adiponectin, TNFα, PAI-1 and fibrinogen

Descriptive statistics will be provided by treatment group for the FAS including geometric mean and 95% confidence intervals for the geometric mean.

9.5.9 PK/PD

Refer to Section 9.5.6

9.6 Sample size calculation

Expected event rates in a secondary prevention trial in patients with prior MI

In spite of differences in eligibility criteria and outcome definitions, several recent trials provide useful information on the expected rates of the endpoint in the proposed trial, and support the focus on hard endpoints. The ARISE trial (Tardif et al. 2008) randomized 6,144 patients with recent acute coronary syndrome (between 14 and 365 days before enrollment) to

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succinobucol vs. placebo and followed them for an average of 2 years. The observed incidence on the composite endpoint of cardiovascular death, MI, stroke or cardiac arrest corresponds to an incidence rate of 5.1 events per 100 person-years.

The PROVE-IT TIMI-22 trial (Cannon et al. 2004) provides an additional estimate of event rates in post-acute coronary syndrome patients (71% post MI), randomized within less than 10 days post index event. Over an average follow-up of 2 years, the 2,099 patients in that trial randomized to receive 80 mg of atorvastatin daily had a cumulative incidence of myocardial infarction or death from coronary heart disease of 7.2%. This corresponds to an incidence rate of 3.7 events per 100 person-years. The addition of stroke and other cardiovascular deaths to this endpoint might be expected to increase this rate to over 4 events per 100 person-years.

The WIZARD trial (O'Connor et al. 2003) provides an additional estimate of event rates based on somewhat different eligibility criteria. That trial randomized individuals with a history of myocardial infarction anytime in the past who also had a C pneumoniae IgG titer of 1:16 or more to azithromycin or placebo and followed these people for an average of 14 months. In 7,722 patients followed for the endpoint of recurrent myocardial infarction or death a total of 600 experienced the event with a median follow up of 14 months, corresponding to an incidence rate of 6.7 events per 100 person-years.

Levels of hsCRP in patients with prior myocardial infarction are powerful predictors of subsequent events. Rates of recurrent events are 30% to 60% higher in patients with hsCRP≥2 mg/L relative to lower levels, regardless of the intensity of statin treatment (Ridker et al. 1998). While aggressive lipid-lowering with statins reduces levels of hsCRP, elevations remain common in post-MI patients. Specifically, in the PROVE-IT TIMI-22 trial, 43% of patients randomized to 80 mg atorvastatin daily had on-treatment levels of hsCRP ≥ 2 mg/L (Ridker et al. 2005). A similar prevalence of elevated hsCRP was observed in patients treated with 80 mg simvastatin daily in the Aggrastat-to-Zocor trial (Morrow et al. 2006). In the primary prevention setting of the JUPITER trial (Ridker et al. 2008), 20 mg of rosuvastatin substantially reduced levels of hsCRP from a baseline median of 3.2 mg/L, but on-treatment median levels in the active treatment group remained above 2 mg/L at all follow-up visits.

The event rates from these trials that have included individuals with prior myocardial infarction, with the additional consideration of the increased MACE rate associated with an elevated level of hsCRP, appear to support an estimate of the expected MACE rate of 3.25 to 4 per 100 person-years in the placebo group. This range already takes into consideration that full-dose statin therapy will most likely be used by such patients. The expected risk during the first year of the trial is expected to be higher for patients randomized within 30 days to 6 months of their index MI, than for patients randomized longer after their index MI.

Needed number of patients with primary endpoints and Sample size

As shown in Table 9-1 694 patients across all three trial arms with an observed major cardiovascular disease event (MACE) provide 90% power for demonstrating the superiority of at least one dose of canakinumab over placebo using the closed testing described in Section 9.4 Analysis of the primary variable (s). at the one-sided 2.45% level available for the final analysis if both doses have a true 23.9% net relative hazard reduction compared to placebo for MACEs after discounting for discontinuations of treatment. This power remains

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close to 80% if one of the two arms is less effective and only has a relative hazard reduction of 15%.

Table 9-1 Power at the final analysis for 694 patients with a MACE

Relative Risk Reduction 150 mg (%)	Relative Risk Reduction 50 mg (%)	**Power to have at least one dose significant**	Power for 150 mg dose (%)	Power for 50 mg dose (%)	Power to have both doses significant
23.9	23.9	**90**	78	81	69
23.9	20	**85**	78	64	57
23.9	15	**79**	77	39	36
23.9	10	**77**	76	19	18
23.9	5	**75**	75	7	7
23.9	0	**74**	74	NA	NA
0	23.9	**74**	NA	74	NA
20	20	**85**	59	62	46
15	15	**48**	33	35	20

Power results are based on 500,000 simulated trials per scenario. Only results for primary endpoints were simulated, therefore the actual power will be slightly higher as significant key secondary endpoints for one dose may make more alpha available for the primary endpoint of the other dose.
All simulations were performed in SAS 9.2 (TS1M0) on an AIX 6.1 platform.

Depending on the exact distribution of endpoints across the three trial arms at least one canakinumab arm needs to achieve a relative hazard reduction compared to placebo of approximately 18 to 19% in order to result in a significant result at the final analysis.

To estimate the sample size and follow-up time required to achieve this number of patients with events, a piecewise exponential distribution for the time to MACE variable with hazard rates in the placebo arm of 4.5% for the first year and 3% yearly for subsequent years was assumed. These hazard rates correspond to a cumulative incidence rate of 4.4% at the end of the first year, and 7.2% at the end of the second year. Furthermore a patient accrual period of 1.5 years, a total study length (including the patient accrual period) of 4.5 years and a cumulative rate of patients lost to follow up of 15% were assumed. Under these assumptions, a sample size of 7,302 randomized patients (in 1:1:1 allocation ratio to canakinumab 150 mg quarterly dose, canakinumab 50 mg quarterly dose and placebo) is expected to be sufficient to accrue the planned number of patients with a MACE.

In order to achieve the planned number of events and preserve the target power of the study the event rate of the primary endpoint will be monitored in a blinded fashion so that adjustments can be made to the number of patients to be randomized and/or the duration of follow-up.

9.7 Power for analysis of key secondary variables

Secondary CV composite endpoint and new onset of diabetes

The majority of events for the key secondary composite endpoint of MACE or hospitalization due to unstable angina requiring revascularization are expected to come from its MACE component. It will be assumed that the additional component will constitute 15% of the

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composite endpoint and that the relative hazard reduction is 23.9% for both MACE and hospitalization due to unstable angina requiring revascularization.

Because the inclusion criteria for this trial are such that the pre-diabetic patients are not specifically selected to have elevated post-load plasma glucose concentrations, event rates for new onset of type II diabetes may be expected to be somewhat lower than in the Diabetes Prevention Program (Diabetes Prevention Program Research Group 2002). In that trial they were 11.0 per 100 person-years in the placebo arm, 7.8 per 100 person-years in the metformin group and 4.8 per 100 person years in the life-style group. Additionally the criteria defining the new onset of diabetes endpoint differ adding further uncertainty about event rates. It will be assumed that the event rate in the control arm is 2/3 of that observed in DPP and that canakinumab is as effective as metformin with a 31% relative hazard reduction versus control in preventing or delaying new onset of diabetes. If 35% of the 7,302 patients to be randomized are pre-diabetic and follow-up for diabetes is on average 3¼ years, then on average 343 new onsets of diabetes would be expected to be available for comparing one canakinumab arm versus placebo.

Under these assumptions the power for the secondary composite CV endpoint for the 50 mg dose is 80% and for the 150 mg dose 71% at the final analysis using the pre-specified testing procedure. Correspondingly, the power using the pre-specified testing procedure for the new onset of diabetes endpoint would be 74% for the 50 mg dose and 64% for the 150 mg dose. Should the rate of new onset of diabetes in the control arm be higher, then the power for the new onset of diabetes endpoint would be higher; should the rate of new onset of diabetes in the control arm be lower, then the power would be lower. Similarly, should the hospitalization due to unstable angina requiring revascularization component add more patients with events to the secondary composite CV endpoint than assumed, the power for that endpoint would be higher as long as the respective canakinumab dose has the assumed effect on the unstable angina requiring revascularization component of the composite.

The lower power for the key secondary endpoints of the 150 mg dose as opposed to those for the 50 mg dose is a consequence the chosen asymmetric testing procedure, which prioritizes the secondary endpoints for the 50 mg dose once the 50 mg dose has been shown to be efficacious, but tries to establish the efficacy of the 50 mg dose even after the 150 mg dose has been shown to be efficacious as explained in Section 9.4.2.

9.8 Interim analyses

Interim analyses of efficacy, futility and safety will be carried out during the study. Two interim analyses of efficacy will be performed when about 50% of the target number of primary cardiovascular events have been accumulated and the second one when 75% of the planned number of events are available. Criteria for the interim and final analyses will be determined using a fixed Bonferroni split of the alpha allocated to the interim analyses and to the final analyses in order to protect the overall one-sided familywise type I error rate across all analyses at 2.5%. The fixed total one-sided alpha allocated to both interim analyses of efficacy combined is 0.05%. Of this 0.01% is allocated to the first efficacy interim analysis and 0.04% allocated to the second efficacy interim analysis. The one-sided significance level for the final analysis is thus 2.45%.

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Interim analyses for futility will be conducted simultaneously with the two analyses of efficacy. It should be noted that the efficacy criteria are not modified to "buy back" alpha based upon the presence of futility boundaries; this conservative approach ensures that the familywise type I error rate of the study is protected.

Full details on boundaries and stopping rules will be pre-specified in the Charter of the Data Monitoring Committee (DMC). Timing and number of safety analyses will also be specified in DMC charter.

The first interim analysis for efficacy will also include T2DM related glucose control data (exploratory endpoint parameters HbA1c, FPG and HOMA) in patients with a diagnosis of T2DM at baseline. The unblinded results of the first interim analysis on T2DM related glucose control data will be reviewed by the DMC. These results will be shared with a senior Novartis representative, the Global Head of the CVM Franchise, and Senior Management for the purpose of planning canakinumab development outside this trial and CV indications (see Section 3.5). The study team and anyone with direct contact with study sites or involved with study assessments or monitoring will be kept blinded to these results. The data shared will be on a summary level to not allow identification of the treatment assignment of individual patients and will not contain information on the primary or key secondary endpoints.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

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This study includes an optional pharmacogenetic component which requires a separate signature if the patient agrees to participate. It is required as part of this protocol that the Investigator presents this option to the patient. The process for obtaining informed consent should be exactly the same as described above for the main informed consent.

Declining to participate in this pharmacogenetic assessment will in no way affect the patient's ability to participate in the main research study.

In the event that Novartis wants to perform testing on the samples that are not described in this protocol, additional Institutional Review Board and/or ethics committee approval will be obtained.

10.3 Responsibilities of the investigator and IRB/IEC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be submitted for publication and posted in a publicly accessible database of clinical study results regardless of study outcome.

11 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the trial to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC. Only amendments that are required for patient safety may be implemented prior to IRB/IEC approval. Notwithstanding the need for approval of formal protocol amendments, the

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investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed within 10 working days.

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Internal Reference Section

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13 Appendix 1: Clinically notable laboratory values and vital signs

Laboratory notable range deviations will be provided in the investigator binder.

Vital sign notable range deviations

VITAL SIGNS		NOTABLE ABNORMALITIES
Pulse (beats/min)		either ≥120 + increase ≥25* or >130 either ≤50 + decrease ≥30* or < 40
Blood pressure (mmHg)	systolic	either ≥180 + increase ≥30* or > 200 either ≤90 + decrease ≥30* or < 75
	diastolic	either ≥105 + increase ≥20* or > 115 either ≤50 + decrease ≥20* or < 40
Weight		a weight change of > 10% during the study

*Refers to post-baseline value as compared to baseline value

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14 Appendix 2 PK / PD Blood Collection Log

Table 14-1 PK / PD Blood Collection Log

Visit	Month	PK(pre-dose)			PD		IG	
		Canakinumab			IL-1β			
		PK Collection #	Sample #	mL	Sample #	mL	Sample #	mL
2	Baseline	1	1	2	101	3	201	2
3	Month 1.5	1	2	2	102	3	202	2
4	Month 3	1	3	2	103	3	203	2
7	Month 12	2	4	2	104	3	204	2
9	Month 18	3	5	2	105	3	205	2
EOS		4	6	2		3	206	2
Washout	EOS + 6	5	7	2	106	3	207	2
Unscheduled Visit			1001, 1002, 1003,		1101, 1102, 1103,		1201, 1202, 1203	,

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15 Appendix 3 Study Endpoint Definitions

15.1 Definition of Cardiovascular Death

Cardiovascular death includes sudden cardiac death, death due to acute myocardial infarction, death due to heart failure, death due to stroke, and death due to other cardiovascular causes.

Sudden cardiac death: A sudden death that occurs in a previously stable patient who does not have a prior terminal condition, such as malignancy not in remission or end-stage chronic lung disease.

Established sudden cardiac death includes the following deaths:

Witnessed and instantaneous without new or worsening symptoms.

Witnessed within 60 minutes of new or worsening symptoms.

Witnessed and attributed to an identified arrhythmia (e.g., captured on ECG recording or witnessed on a monitor by either a medic or paramedic or unwitnessed but found on implantable cardioverter-defibrillator review).

After unsuccessful resuscitation from cardiac arrest

After successfully resuscitated from cardiac arrest and without identification of a non-cardiac etiology (Post-Cardiac arrest Syndrome)

Unwitnessed death without other cause of death

General Considerations

A patient seen alive and clinically stable 12-24 hours prior to being found dead without any evidence or information of a specific cause of death should be classified as an "Unwitnessed Death." Typical scenarios include

• Patient well the previous day but found dead in bed the next day

• Patient found dead at home on the couch with the television on

Deaths for which there is no information beyond "Patient found dead at home" may be classified as "Undetermined Cause of Death"

Death due to Acute Myocardial Infarction (AMI): refers to a death within 30 days after a myocardial infarction (MI) related to consequences seen immediately after the myocardial infarction, such as progressive congestive heart failure (CHF), inadequate cardiac output, or recalcitrant arrhythmia. If these events occur after a "break" (e.g., a CHF and arrhythmia free period), they should be designated by the immediate cause. The acute myocardial infarction should be verified either by the diagnostic criteria outlined for acute myocardial infarction or by autopsy findings showing recent myocardial infarction or recent coronary thrombus, and there should be no conclusive evidence of another cause of death.

Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of

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cardiac biomarkers in the blood should be considered death due to acute myocardial infarction.

If death occurs before biochemical confirmation of myocardial necrosis can be obtained, adjudication should be based on clinical presentation and ECG evidence.

Death resulting from a procedure to treat myocardial ischemia or to treat a complication resulting from myocardial infarction should also be considered death due to acute MI.

Death due to a myocardial infarction that occurs as a direct consequence of a cardiovascular investigation/procedure/operation should be classified as death due to other cardiovascular cause.

Death due to Heart Failure or Cardiogenic Shock: refers to death occurring in the context of clinically worsening symptoms and/or signs of heart without evidence of another cause of death.

Death due to Heart Failure or Cardiogenic shock should include sudden death occurring during an admission for worsening heart failure as well as death from progressive heart failure or cardiogenic shock following implantation of a mechanical assist device.

New or worsening signs and/or symptoms of congestive heart failure (CHF) include any of the following:

- New or increasing symptoms and/or signs of heart failure requiring the initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving maximal therapy for heart failure
- Heart failure symptoms or signs requiring continuous intravenous therapy or chronic oxygen administration for hypoxia due to pulmonary edema
- Confinement to bed predominantly due to heart failure symptoms
- Pulmonary edema sufficient to cause tachypnea and distress not occurring in the context of an acute myocardial infarction, worsening renal function, or as the consequence of an arrhythmia occurring in the absence of worsening heart failure
- Cardiogenic shock not occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure.

Cardiogenic shock is defined as systolic blood pressure (SBP) < 90 mm Hg for greater than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion:

- Cool, clammy skin *or*
- Oliguria (urine output < 30 mL/hour) *or*
- Altered sensorium *or*
- Cardiac index < 2.2 L/min/m2

Cardiogenic shock can also be defined if SBP < 90 mm Hg and increases to ≥ 90 mm Hg in less than 1 hour with positive inotropic or vasopressor agents alone and/or with mechanical support.

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Death due to Stroke (intracranial hemorrhage or non-hemorrhagic stroke): refers to death occurring up to 30 days after a suspected stroke based on clinical signs and symptoms as well as neuroimaging and/or autopsy, and where there is no conclusive evidence of another cause of death.

Death due to Other Cardiovascular Causes: refers to death due to a cardiovascular cause not
included in the above categories (e.g. dysrhythmia, pulmonary embolism, cardiovascular intervention, aortic aneurysm rupture, or peripheral arterial disease). Mortal complications of cardiac surgery or non-surgical revascularization, even if "non-cardiovascular" in nature, should be classified as cardiovascular deaths.

Death of Undetermined Cause (presumed cardiovascular) :
All deaths not attributed to the categories of Cardiovascular Death or to a Non-cardiovascular cause are considered presumed cardiovascular deaths.

15.2 Non-cardiovascular death

Non-Cardiovascular death is defined as any death not covered by cardiac death or vascular death and is categorized as follows:

Pulmonary causes
Renal causes
Gastrointestinal causes
Infection (including sepsis)
Non-infectious causes
Malignancy
Accident/Trauma
Suicide
Non-cardiovascular system organ failure (e.g. Hepatic)
Hemorrhage, not intracranial
Other. Please specify.

15.3 Definition of Non-fatal Myocardial Infarction

Acute Myocardial Infarction : the term myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for MI.

Spontaneous MI : Detection of rise and/or fall of cardiac biomarkers with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:

- Symptoms of ischemia
- ECG changes indicative of new ischemia (new ST-T changes or new LBBB)*
- Development of pathological Q waves in the ECG**
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

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- *ECG manifestation of acute myocardial ischemia (in the absence of LVH and LBBB):
- ST Elevation - New ST elevation at the J-point in two contiguous leads with the cut-off points:
- ≥ 0.2 mV in men or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads.
- ST depression and T-wave changes – New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or T inversion ≥ 0.1 mV in two contiguous leads with prominent R waves or R/S ratio >1.
- **Pathological Q waves:
  1. Any Q-wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3
  2. Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 an any two leads of a contiguous lead grouping (I, aVL, V6, V4-V6, II, III, aVF).

Percutaneous Coronary Intervention (PCI) related Myocardial Infarct ; For PCI in patients with normal baseline troponin values elevations of cardiac biomarkers above the 99th percentile URL within 24 hours of the procedure are indicative of peri-procedural myocardial necrosis. By convention increases of biomarkers greater than 3 x 99th percentile URL are consistent with PCI related myocardial infarction.

- If the cardiac biomarker is elevated prior to PCI a ≥ 20% increase of the value in that second cardiac biomarker within 24 hours of the PCI and documentation that cardiac biomarkers were decreasing (two samples at least 6 hours apart) prior to the suspected recurrent MI is also consistent with PCI related MI.
- Symptoms of cardiac ischemia are not required

CABG related Myocardial Infarct : Either new pathological Q waves in at least 2 contiguous leads on the ECG that persist through 30days or new LBBB

OR

Angiographically documented new graft or native coronary artery occlusion

OR

Imaging evidence of new loss of viable myocardium

Is consistent with CABG related Myocardial Infarct.

If the cardiac biomarker is elevated prior to CABG a ≥ 20% increase of the value in the second cardiac biomarker within 72 hours of CABG AND documentation that the cardiac biomarkers were decreasing (2 samples at least 6 hours apart) prior to the suspected recurrent MI plus either new pathological Q waves in at least 2 contiguous leads on the ECG or new LBBB, angiographically documented new graft or native artery occlusion or imaging evidence or new loss of viable myocardium is consistent with a peri-procedural myocardial infarct after CABG.

Symptoms of cardiac ischemia are not required.

Criteria for Prior Myocardial Infarction : Any of the following criteria meets the diagnosis for prior myocardial infarction:

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- Development of new pathological Q waves with or without symptoms
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract in the absence of a non-ischemic cause
- Pathological findings of a healed or healing myocardial infarction

ECG changes associated with prior Myocardial Infarction:

- Any Q wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3
- Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6, V4-V6, II, III, and aVF)
- R-wave ≥ 0.04 seconds in V1-V2 and R/S ≥ 1 with a concordant positive T-wave in the absence of a conduction defect

Criterion for Reinfarction : In patients where recurrent MI is suspected from clinical signs or symptoms following the initial infarction, an immediate measurement of the employed cardiac biomarker is recommended. A second sample should be obtained 3-6 hours later. Recurrent infarction is diagnosed if there is a ≥ 20% increase of the value in the second sample. This value should exceed the 99th percentile URL. However if cardiac biomarkers are elevated prior to the suspected new MI, there must also be documentation of decreasing values (two samples at least 6 hours apart) prior to the suspected new MI. If the values are falling criteria for reinfarction by further measurement of biomarkers together with features of the ECG or imaging can be applied.

ECG diagnosis of reinfarction following the initial infarction : may be confounded by the initial evolutionary ECG changes. Reinfarction should be considered when the ST elevation ≥ 0.1 mV reoccurs in an inpatient having a lesser degree of ST elevation or new pathognomonic Q-waves, in at least two contiguous leads, particularly when associated with ischemic symptoms for 10 minutes or longer, The re-evaluation of the ST segment can, however also be seen in threatening myocardial rupture and should lead to additional diagnostic work-up. ST depression or LBBB on their own should not be considered valid criteria for Myocardial Infarction.

If biomarkers are increasing or peak is not reached then there is insufficient data to diagnose recurrent MI.

Clinical Classification of different types of Myocardial Infarction :For each MI identified a Type of MI will be assigned using the following guidelines:

- Type 1 – Spontaneous MI related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring or disSection.
- Type 2 – MI secondary to ischemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, anemia, hypotension, coronary embolism, arrhythmias, hypertension or hypotension.
- Type 3 –Sudden unexpected cardiac death including cardiac arrest, often with symptoms suggestive of myocardial ischemia accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained or at a time before the appearance of cardiac biomarkers in the blood.

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- Type 4a –MI associated with PCI.
- Type 4b –MI associated with stent thrombosis as documented by autopsy or angiography.
- Type 5 –MI associated with CABG.

Silent MI

The following criteria will be used by the central ECG reading vendor to define interval "silent" (no clinical symptoms or signs) MI between baseline and yearly ECGs:

Criteria for MI (Surawcz, Ed : Chou's Electrocardiography in Clinical Practice, 5th Edition, 2001).

Myocardial infarctions are reported only on the basis of pathologic Q waves. Pathologic Q waves are defined as Q wave duration > 40ms **and** Q/R ratio = 1/3.

Any Q wave in V1 or V2 that is followed by an R wave should be considered abnormal.

When pathologic Q waves (i.e., myocardial infarction) are present, ST elevation or T wave inversion may be used to classify the infraction as New or Acute. However, ST elevation or T wave inversion in the absence of pathologic Q waves are not sufficient criteria for diagnosis of myocardial infarction.

- **Anterolateral MI** - Pathologic Q waves in leads V3-V6.
- **Anterior MI** - Pathologic Q waves in V3 and V4.
- **Anteroseptal MI** - Pathologic Q waves or QS in leads V1-V4.
- **Extensive Anterior MI** - Pathologic Q waves in leads I, aVL, and V1-V6.
- **High lateral MI** - Pathologic Q waves in leads I and aVL.
- **Inferior MI** - Pathologic Q waves or QS in at least two of the inferior leads: aVF, III, II.
- **Lateral MI** - Pathologic Q waves in leads I, aVL, and V5-V6.
- **Septal MI** - Pathologic Q waves or QS in leads V1-V2, (V3). **In the presence of LAHB or LVH a Q or QS in V3 is required.**
- **Posterior MI** - Initial R wave duration 40 ms in V1 or V2, and R > S and upright T wave; Inferior or Lateral MI are usually also present.

New MI

These criteria for MI are more stringent than the Expert Consensus Document criteria, requiring Q waves to be $\geq$ 0.04 sec in duration and an R/S ratio $\geq$ 1/3. These criteria (drawn from the cardiology literature) are designed to minimize the false positive detection of MIs due to very small physiologic Q waves in the inferior and anterolateral leads.

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15.4 Definition of Stroke

Stroke: is defined as the rapid onset of a new persistent neurological deficit attributed to an obstruction in cerebral blood flow and/or cerebral hemorrhage with no apparent non-vascular cause (e.g. tumor, trauma, infection). Available neuroimaging studies will be considered to support the clinical impression and to determine if there is a demonstrable lesion compatible with an acute stroke. Non-fatal strokes will be classified as ischemic, hemorrhagic or unknown.

For the diagnosis of Stroke, the following 4 criteria should be fulfilled:

1. Rapid onset* of a focal/global neurological deficit with at least one of the following:

   Change in level of consciousness

   Hemiplegia

   Hemiparesis

   Numbness or sensory loss affecting one side of the body

   Dysphasia/aphasia

   Hemianopsia

   Amaurosis Fugax

   Other new neurological sign/symptom(s) consistent with stroke

   *if the mode of onset is uncertain, a diagnosis of stroke may be made provided that there are no plausible non-stroke causes for the clinical presentation.

2. Duration of a focal/global neurological deficit:

   ≥ 24 hours

   OR

   < 24 hours if:

   This is because of at least one of the following interventions

Pharmacologic (i.e. Thrombolytic drug administration)
Non-pharmacologic (i.e. Neurointerventional procedure (e.g. Intracranial angioplasty)

OR

3. Available brain imaging clearly documents a new hemorrhage infarct

   OR

4. The neurological deficit results in death.

No other readily identifiable non-stroke cause for the clinical presentation (e.g. Brain tumor, trauma, infection, hypoglycemia, peripheral lesion)

Confirmation of the diagnosis by at least on of the following:

Neurology or neurosurgical specialist

Brain imaging procedure (at least one of the following):

i. CT scan

ii. MRI scan

iii. Cerebral vessel angiography

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Lumbar puncture (i.e. Spinal fluid analysis diagnostic of intracranial hemorrhage)

If the acute focal signs represent a worsening of a previous deficit, these signs must have either:

- Persisted for more than one week or
- Persisted for more than 24 hours and were accompanied by an appropriate new MRI or CT scan finding

Strokes are sub-classified as follows:

Ischemic (non-hemorrhagic): A stroke caused by an arterial occlusion due to either a thrombotic) e.g. Large vessel disease/atherosclerotic or small vessel/lacunar) or embolic etiology

Hemorrhagic: A stroke due to a hemorrhage in the brain as documented by neuroimaging or autopsy. This category will include strokes due to primary intracerebral hemorrhage (intraparenchymal or intraventricular), ischemic strokes with hemorrhagic transformation (i.e.; no evidence or hemorrhage on an initial imaging study but appearance on a subsequent scan), subdural hematoma*, and primary subarachnoid hemorrhage.

*All subdural hematomas that develop during the clinical trial : should be recorded and classified as either traumatic versus non traumatic.

Unknown: the stroke type could not be determined by imaging or other means (e.g. Lumbar puncture, neurosurgery, or autopsy) or no imaging was performed

Stroke Disability

Stroke disability can be classified using an adaptation of the modified Rankin Scale as follows:

0: No symptoms at all

1: No significant disability despite symptoms; able to carry out all usual duties and activities

2: Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance

3 : Moderate disability; requiring some help, but able to walk without assistance

4 : Moderately severe disability; unable to walk without assistance and unable to attend toown bodily needs without assistance

5. Severe disability; bedridden, incontinent and requiring constant nursing care and attention

6. Dead

15.5 Definition of Stent Thrombosis

1. Stent Thrombosis: Timing:

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Type	Timing
Acute stent thrombosis*	0 to 24 hours after stent implantation
Subacute stent thrombosis	> 24 hours to 30 days after stent implantation
Late stent thrombosis†	> 30 days to 1 year after stent implantation
Very late stent thrombosis†	> 1 year after stent implantation

Stent thrombosis should be reported as a cumulative value over time and at the various individual time points specified above. Time 0 is defined as the time point after the guiding catheter has been removed and the patient has left the catheterization laboratory.

***Acute or subacute can also be replaced by the term early stent thrombosis. Early stent thrombosis (0 to 30 days) will be used in the remainder of this document.**

†Includes primary as well as secondary late stent thrombosis; secondary late stent thrombosis is a stent thrombosis after a target lesion revascularization.

2. ARC Definitions of Definite, *Probable and Possible Stent Thrombosis

Definite Stent Thrombosis

Definite stent thrombosis is considered to have occurred by either angiographic or pathological confirmation:

a. Angiographic confirmation of stent thrombosis : The presence of a thrombus that originates in the stent or in the segment 5mm proximal or distal to the stent and presence of at least 1 of the following within a 48 hour time window:

1. Acute onset of ischemic symptoms at rest

2. New ischemic ECG changes that suggest acute ischemia

3. Typical rise and fall in cardiac biomarkers

4. Non-occlusive thrombus :

a. Intracoronary thrombus is defined as a (spherical, ovoid or irregular) non calcified filling defector lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections or persistence or contrast material within the lumen, or a visible embolization or intraluminal material downstream.

5. Occlusive thrombus

a. TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch)

b. Pathological confirmation of stent thrombosis. Evidence of recent thrombosis within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy.

Probable Stent Thrombosis

Clinical definition of probable stent stenosis is considered to have occurred after intracoronary stenting in the following cases:

a. Any unexplained death within the first 30 days

b. Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other cause.

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15.6 Definition of Unstable Angina Requiring Unplanned Revascularization

Unstable Angina requiring Unplanned Revascularization is defined as :

No elevation in cardiac biomarkers

and

Clinical presentation (one of the following) with cardiac symptoms lasting ≥10 minutes and considered to be myocardial ischemia on final diagnosis

- Rest angina or
- New onset (<2 months) severe angina (CCS* classification severity ≥ III) or
- Increasing angina (in intensity, duration and/or frequency) with an increase in severity of at least 1 CCS class to at least CCS III

and

Severe recurrent ischemia requiring urgent revascularization: as defined by an episode of angina prompting the performance of coronary revascularization on the index hospitalization

or

An episode of recurrent angina after discharge that resulted in re-hospitalization

during which coronary revascularization was performed.

and

At least one of the following:

- New or worsening ST or T segment changes on ECG. ECG changes should satisfy the following criteria for AMI in the absence of LVH and LBBB
- ST Elevation - New ST elevation at the J point in two anatomically contiguous leads with the cut-off points: ≥ 0.2 mV in men (> 0.25 mV in men < 40 years) or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads.
- ST depression and T-wave changes – New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or new T inversion ≥ 0.1 mV in two contiguous leads.
- Evidence of ischemia on stress testing with cardiac imaging.
- Evidence of ischemia on stress testing without cardiac imaging but with angiographic evidence of ≥ 70% lesion, and/or thrombus in the epicardial coronary artery or initiation/increased dosing of anti-anginal therapy.
- Angiographic evidence of ≥ 70% lesion and/or thrombus in an epicardial coronary artery.

*Grading of Angina Pectoris According to Canadian Cardiovascular Society Classification

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Class	Description of Stage
Class I	"Ordinary physical activity does not cause . . . angina," such as walking or climbing stairs. Angina occurs with strenuous, rapid, or prolonged exertion at work or recreation
Class II	"Slight limitation of ordinary activity." Angina occurs on walking or climbing stairs rapidly; walking uphill; walking or stair climbing after meals; in cold, in wind, or under emotional stress; or only during the few hours after awakening. Angina occurs on walking more than 2 blocks on the level and climbing more than 1 flight of ordinary stairs at a normal pace and under normal conditions.
Class III	"Marked limitations of ordinary physical activity." Angina occurs on walking 1 to 2 blocks on the level and climbing 1 flight of stairs under normal conditions and at a normal pace.
Class IV	"Inability to carry on any physical activity without discomfort—anginal symptoms may be present at rest."

15.7 Definition of Heart Failure requiring Hospitalization

Heart failure requiring hospitalization is defined as an event that meets the following criteria:

Requires hospitalization defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 12 hour stay (or a date change if the time of admission/discharge is not available)

AND

Clinical manifestation of heart failure including at least one of the following: New or worsening:

dyspnea,

orthopnea,

paroxysmal nocturnal dyspnea,

edema,

pulmonary basilar crackles,

radiological evidence of worsening heart failure.

AND

Additional/increased therapy

Initiation of IV loop diuretic, inotrope or vasodilator therapy

Uptitration of IV therapy, if already on therapy

Initiation of mechanical or surgical intervention, or use of ultra-filtration, hemofiltration or dialysis that is specifically directed at the treatment of heart failure.

Biomarker results (e.g. brain natriuretic peptide) consistent with congestive heart failure will be supportive of this diagnosis.

15.8 Definition of New Onset Diabetes

The clinical definition of Type 2 diabetes consists of the following:

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a. Presence of Fasting Plasma Glucose measured on two consecutive occasions $\geq$ 126 mg/dl (the Event Date will be the first of these two occasions)

Or

b. Presence of HbA1c measured on two consecutive occasions $\geq$ 6.5 % in a laboratory which has validated compliance of a test that conforms to the National Glycosylation Standards Program (Little et al 2010) reference measurement of HbA1c (the Event Date will be the first of these two occasions)

Or

c. The institution and use of a diabetes medication for the purpose of glucose control by the patient including all oral agents, insulin, and injectable GLP-1 analogs. (the Event Date will be the Date noted on the prescription)

d. In the event wherein a patient has one laboratory parameter which would place them in the NOD category if repeated and confirmed, then has a subsequent measurement another parameter which similarly would place them in the NOD category if repeated and confirmed (e.g. FPG $\geq$ 126 mg/ dl followed by HbA1c $\geq$ 6.5%, or vice versa) will be considered to have NOD (the Event Date will be the first of these 2 occasions).

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15.9 Definition of Transient Ischemic Attack

A Transient Ischemic Attack is defined as change in the blood supply to a particular area of the brain, spinal cord, or retina, resulting in brief neurologic dysfunction that persists, by definition, for less than 24 hours

Symptoms and signs

New and focal neurologic sensory and/ or motor deficits which have a rapid onset, last no more than 24 hours and resolve completely. Symptoms may be localized to brain, spinal cord, or retina, relative to the vascular supply affecting neurologic function.

Focal sensory, reflexes, and motor lesions which are manifestations of the arterial structure from which the insufficiency arises. All new neurologic signs resolve completely within 24 hours from the time of onset.

- Hemiplegia/paresis
- Hemianaesthesia/sensory deficit
- Hemianopsia
- Neglect
- Isolated facial weakness/droop
- Ataxia/dysmetria
- Dysarthria/speech impairment
- Aphasia
- Other

Procedure

A CT , MRI, or MRA of the brain which demonstrates no new pathology. A neurological or neurosurgical consultation may accompany the imaging study or studies, but is not required for the diagnosis of TIA.

15.10 Definition of Critical Limb Ischemia

Critical limb ischemia is a manifestation of occlusive peripheral arterial disease that describes patients with chronic occlusive disease who demonstrate ischemic rest pain or ischemic skin lesions (either ulcers or gangrene).

Symptoms

Pain at rest, claudication, recurrent skin lesions are common.

Signs

Coolness to touch and pallor of the involved extremity may be present. Diminution or absence of pulse to palpation or bedside Doppler examination. Ulcers of the skin may be present.

Procedure

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CT, MRI, MRA or angiography may be performed for diagnostic purposes. Angiographic or open revascularization may be attempted to improve arterial blood flow.

15.11 Definition of Limb Amputation due to Vascular Cause

Therapeutic reSection of a limb or a portion of a limb due to a combination of vascular insufficiency, osteomyelitis, cellulitis / gangrene, or poor wound healing.

Symptoms

Symptoms may include claudication, rest pain, fever, recurrent infections. There may be a history of previous partial or complete amputations.

Signs

Decreased arterial pulse, abnormal temperature, deformity, chronic skin ulceration

Procedure

Therapeutic reSection of the pathologic extremity. Reasons for amputation:

- Vascular insufficiency
- Osteomyelitis
- Cellulitis
- Gangrene
- Poor healing post-surgical wound
- Poor healing post trauma

15.12 Definition of Non-coronary Revascularization

Non-coronary revascularization is defined as vascular surgery or percutaneous intervention. Vascular surgery is defined as the placement of a conduit with or without proximal and/or distal anastamoses. Percutaneous intervention is defined as balloon inflation with or without stenting.

Symptoms

Symptoms will be specific to the arterial vasculature involved and the time of course of development of the occlusion(s).

Signs

Signs will be specific to the arterial vasculature involved and the time of course of development of the occlusion(s).

Procedures

Diagnostic CT, MRI, MRA, or Doppler US may be performed.

Revascularization or attempted revascularization with or without stenting including carotid surgery, peripheral vascular surgery or PCI, including abdominal aortic aneurysm repair, carotid revascularization, femoral, popliteal iliac, renal, open or percutaneous peripheral interventions depending on the site definition of Supraventricular Tachycardia / Atrial Fibrillation

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Supraventricular tachycardia includes abnormal sinus tachycardia, ectopic atrial tachycardia atrial fibrillation/atrial flutter (with rapid ventricular response) and junctional tachycardia.

Symptoms

Symptoms may include palpitations, dyspnea, chest pain, dizziness, numbness or loss of consciousness.

Signs

Rapid heart rate which may be regular or irregular. Peripheral pulses may be diminished or absent.

Procedure

ECG (required) demonstrates narrow complex tachycardia originating from a site (or sites) above the ventricles. P waves may or may not be present, depending on the specific type of SVT.

15.13 Definition of DVT

Deep vein thrombosis is defined as the pathologic presence of thrombus with inflammation which affects the leg veins (such as the femoral vein or the popliteal vein), the deep veins of the pelvis, or rarely an upper extremity vein.

Symptoms

There may be no symptoms referable to the location of the DVT, but the classical symptoms of DVT include pain, swelling and redness of the leg and dilation of the surface veins

Signs

DVT include pain, swelling and redness of the leg and dilation of the surface veins may be present. Homan's sign, posterior calf pain on foot dorsiflexion may be present but is an insensitive indicator. Commonly, no signs are present.

Procedure

Duplex Ultrasonography is the most commonly used diagnostic test. Other tests may include d-dimer blood testing, CT with contrast, and infrequently venography. Confirmation by diagnostic study required.

15.14 Definition of PE

A Pulmonary Embolism is defined as an acute blockage of one or more pulmonary arteries by an embolus which has originated elsewhere (usually venous thrombus) and traveled through the venous system to reach the pulmonary arteries.

Symptoms

Symptoms may include sudden-onset dyspnea, tachypnea), chest pleuritic chest pain, cough, and hemoptysis.

Signs

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In addition, severe cases can include signs such as cyanosis, tachycardia, hypotension, and syncope.

Procedure

Chest X-Rays may be performed but are rarely diagnostic. Blood testing for d-dimer is often used to screen prior to performing medical imaging. Spiral CT of the chest is often performed. If significant pathology makes spiral CT less useful, a ventilation perfusion scan of the chest may be available. Confirmation by diagnostic study and localization (left or right lung and lobe) required.

15.15 Definition of Coronary Angiography

Coronary angiography is an invasive procedure wherein radiocontrast dye is introduced via an arterial catheter into the aorta, left ventricle, and coronary arteries to examine the functional capacity and anatomy of these entities.

Procedure

A radiocontrast dye is adminstered as described above by a cardiologist or invasive radiologist, using peripheral access into an artery (femoral or brachial).

15.16 Definition of Coronary Revascularization

Coronary revascularization is an invasive procedure which usually follows coronary angiography, wherein either Percutaneous Transluminal Intervention, followed by Stent Placement, Balloon Angioplasty, or CABG is performed to relieve obstructed coronary arteries.

Procedure

A team of medical professionals lead by either an invasive cardiologist (Percutaneous Transluminal Intervention, followed by Stent Placement, Balloon Angioplasty,) or a thoracic surgeon (CABG), who performs the described procedures.

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Clinical Development

ACZ885M/Canakinumab

Clinical Trial Protocol CACZ885M2301

A randomized, double-blind, placebo-controlled, event-driven trial of quarterly subcutaneous canakinumab in the prevention of recurrent cardiovascular events among stable post-myocardial infarction patients with elevated hsCRP

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List of abbreviations

ADL	Activities of Daily Living
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
CABG	Coronary Artery Bypass Graft
CAPS	Cryopyrin-Associated Periodic Syndromes
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
CRF	Case Report/Record Form
CPO	Country Pharma Organization
CRO	Contract Research Organization
CV	Cardiovascular
CVD	Cardiovascular Disease
DAR	Dose Administration Record
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
DS&E	Drug Safety and Epidemiology
eCRF	electronic Case Report/Record Form
ECG	Electrocardiogram
EDC	Electronic Data Capture
eGFR	estimated Glomerular Filtration Rate
EOS	End of Study
EQ-5D	Euro QoL five dimensions questionnaire
FAS	Full Analysis Set
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
GWA	Genome-wide association
HbA1c	Glycosylated hemoglobin
HDL	High-Density Lipoprotein
HIV	Human Immunodeficiency Virus

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hsCRP	High Sensitivity C-Reactive Protein
IA	Interim Analysis
IAC	Infection Adjudication Committee
IB	Investigators Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IG	Immunogenicity
IL-1β	Interleukin 1 Beta
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
i.v.	intravenous
IVRS/IWRS	Interactive Voice Response System/ Interactive Web Response System
LDL	Low density lipoprotein
LFT	Liver Function Test
MACE	Major Adverse Cardiovascular Event
MedDRA	Medical dictionary for regulatory activities
MFSI-SF	Multi Dimensional Fatigue Symptom Inventory-Short Form
MI	Myocardial Infarction
MRS	Modified Rankin Scale
NOD	New Onset Diabetes
NYHA	New York Heart Association
OC/RDC	Oracle Clinical/Remote Data Capture
PCI	Percutaneous coronary intervention
PCP	Primary Care Physician
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per Protocol Set
PPD	Purified protein derivative
PRO	Patient Reported Outcomes
PTCA	Percutaneous transluminal coronary angioplasty

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PVD	Peripheral Vascular Disease
QFT-g	QuantiFERON-TB Gold
QoL	Quality of Life
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SBP	Systolic Blood Pressure
s.c.	Subcutaneous
SF-36	Short Form (36) Health Survey
SOC	System Organ Class
SIS-16	Stroke Impact Scale
SMQ	Standardized MedDRA Queries
SUSAR	Suspected Unexpected Serious Adverse Reactions
T2DM	Type 2 Diabetes Mellitus
TB	Tuberculosis
TIA	Transient Ischemic Attack
VLDL	Very-Low-Density Lipoprotein

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Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	A study drug or placebo used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	A portion of the study which serves a specific purpose. Typical epochs are: screening/recruitment, wash-out, treatment, and follow-up
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug.”
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IVR system
Patient number	A number assigned to each patient who enrolls in the study. When combined with the center number, a unique identifier is created for each patient in the study.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Study drug	Any drug administered to the patient as part of the required study procedures; includes investigational drug and any control drugs
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

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Amendment 9

Amendment Rationale

CACZ885M2301 Protocol Amendment 9 provides details for the study extension described in the current protocol. Following accrual of the target number of primary events, eligible patients will have the option to continue study participation in the extension phase at their end of study visit. The objective of the extension phase is to obtain further follow-up information on long-term safety on continued exposure to canakinumab in trial participants. Additionally, as defined in the current protocol, the study drug washout in the cohort of prediabetic patients who did not progress to diabetes during the pivotal phase will assess the durability of any potential antidiabetic effect of canakinumab after discontinuation of therapy. Persistence of a potential effect of canakinumab on quality of life and the impact of a treatment switch to the open-label dose on quality of life will also be explored. Patients who choose to participate will remain on their pivotal phase blinded assigned treatment arm for the first three extension phase visits, except for prediabetic patients who will undergo a 6-month study drug washout by skipping two doses of their pivotal phase blinded assigned treatment arm. After the database from the pivotal study is locked all participants will be switched to an open-label dose of 150 mg canakinumab. The 150 mg dose is predicted to have the highest likelihood of having the most favorable benefit: risk ratio based on biomarker and clinical data from phase II studies in Type 2 diabetics. The final canakinumab dose will be based on the results from the pivotal phase. The transition to an intermediate dose of 150 mg will avoid further placebo treatment until the final dose of canakinumab is implemented at the study sites. The extension phase will continue in an individual country for a minimum of two years from the date of the first patients enrolled in that country. The maximum duration of the extension phase will be 2.5 years from the date of the first patient enrolled in that country or until marketed product is available in that country, whichever comes first. While the extension phase is then deemed complete the safety follow-up is anticipated to be continued in registries following study results and discussion with Health Authorities.

Changes to the protocol

The described changes under the amendment rationale are implemented throughout the protocol.

In addition, the following updates, clarifications and omissions are included in this protocol amendment:

- Implementation of global and local registries post approval will be subject to discussion and agreement with health authorities during Biologic License Application (BLA)/Marketing Authorization Application (MAA) review and will be conducted via separate protocols. Section 5.5.10 updated to reflect this.

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- Section 7.1: described the reporting of adverse events during the extension phase. During the extension phase, endpoints will no longer be collected. Hence, the study specific exemption granted from the Health Authorities not to report study endpoints as serious adverse events/adverse events in the pivotal phase does not apply to the extension phase. During the extension phase ALL adverse events will be reported as AEs following the procedures described in Section 7.1 and Section 7.2.
- Section 7.2: clarification regarding the instructions for Serious Adverse Event (SAE) reporting, allowing also electronic SAE reporting
- Section 7.3 added to describe reporting of study treatment errors including misuse/abuse during the extension phase of the study
- Section 7.6.2 added that the Infections Adjudication Committee will not adjudicate cases during the extension phase
- Section 7.6.3 added that the Malignancy Adjudication Committee will not adjudicate cases during the extension phase
- Section 10.5 added to describe the Quality Management system that applies to this trial.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~strike through red font for deletions~~ and red underlined for insertions. A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, sites are required to submit for approval an updated informed consent that covers the extension phase of the study, which will be signed by patients before they move into main drug dispensing period (Visit 201 and beyond) of the extension phase.

Other minor updates and corrections were also included.

Summary of previous amendments

Amendment 8

Amendment Rationale

CACZ885M2301 Protocol Amendment 8 adjusts the number of patients to be randomized into the study from 17,200 patients to approximately 10,000 patients. This change is not based on safety or efficacy concerns, instead it resulted from a strategic decision that considered the higher than anticipated primary event endpoint rate observed thus far.

Importantly, the study objectives and power remain unchanged and the study will still complete when 1,400 primary event endpoints are accrued as originally planned. The elapsed calendar time to reach the conclusion of the study is now estimated to be approximately 6 years (instead of 5 years) of treatment and follow-up from the start of enrollment in the trial to when 1,400 primary cardiovascular events have been accrued.

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Protocol Amendment 8 also introduces the option to perform a futility analysis earlier than the first planned efficacy interim analysis (IA) (at approximately 50% primary events) but only after a sufficient number of primary events are accrued, i.e., >25%. This may be performed by the DMC in consideration of the longer period of time that may be needed to reach the first IA from the start of enrollment.

Changes to the protocol

The described changes in the amendment rationale are implemented throughout the protocol.

The following minor updates, clarifications and omissions are included in this protocol amendment:

- In accordance with the change in sample size, the total planned patients screened changed from 29,000 to 17,000.
- Spelled out the CANTOS acronym (Section 3.1)
- Informed that CACZ885M2301 Sub-study S1 and S2 have been terminated. Of note, the Sponsor decision to terminate these sub-studies was not due to safety or efficacy concerns (Section 3.1).
- Clarified that the full committee DMC safety reviews will occur on a six-month basis and the DMC chair will review the safety data on a three-month basis (Section 3.5).
- In Section 5.5.8, added information specifying that the patient contact information should be reviewed at each visit and clarified the process for visits/patient contact following study drug discontinuation.
- Added Years 5 and 6 to Table 6-1
- In Section 6.5.7, informed as a correction that Allergies/Immunological are not adjudicated events.
- Corrected the following statement noting that all malignancies including basal cell carcinoma should be reported as SAEs meeting the criteria of "medically significant" (Section 7.1)
- In the site monitoring section (Section 8.1), incorporated the various methods utilized to ensure protocol and GCP compliance and the quality/integrity of the sites' data. Continuous remote monitoring and a central analytics organization have been added as a complement to field monitoring.
- A discussion of the currently observed event rates, the impact on trial duration and the lack of an impact on study power was added to the statistical section.

Other minor updates and corrections were also included.

Amendment 7

Short summary of the amendment rationale and major changes

In order to comply with a Health Authority (PMDA) request from Japan, Visit 1 screening tests for HBc antibody and HBs antibody are added in Japan only to prevent enrolling Japanese patients who have a history of hepatitis B infection and/or are hepatitis B carriers. In

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order to comply with the Central Ethics Committee request in Croatia, specific language regarding post-menopausal status determination in women less than 50 years of age is added for Croatia only.

Additional updates and clarifications were also noted in this protocol amendment such as allowing the prescreen hsCRP if performed at the central laboratory less than 60 days prior to Visit 2 and ≥ 2mg/L to be used as the qualifying hsCRP, clarifying the tuberculosis status determination for study entry, informing that recruitment will target approximately 50% of randomized patients with an index MI 30 days to 12 months prior to randomization and 50% with an index MI >12 months prior to randomization, and noting that for patients whose treatment is stopped as a result of a data monitoring committee recommendation to suspend treatment in one dose group, follow-up for cardiovascular and safety events will continue at 6 month intervals. The amendment also removed mention of a recruitment duration of 21 months and informed that the elapsed calendar to time to reach the conclusion of the study is estimated to be approximately 5 years of treatment from the start of enrollment to the occurrence of when 1,400 patients have had confirmed adjudicated primary cardiovascular events. In Section 5.5.8, additional clarity was added to the situations under which patients may restart study treatment, the liver function test discontinuation criteria was aligned with recent company guidance for liver enzyme elevations, and it was noted that patients who develop any malignancy other than excised basal cell skin carcinoma must discontinue from study treatment. Lastly, the Immunogenicity methodology was updated, the total vascular events composite was corrected to include coronary angiogram, and the amendment informed of two separate adjudication committees (Infection and Malignancy) to replace the previously described Allergy, Infection and Malignancy Adjudication committee.

Other minor updates and corrections were also included.

Amendment 6

Short summary of the amendment rationale and major changes

Following Health Authority feedback on the doses, Amendment 6 included a lower 50 mg dose arm in order to examine canakinumab's dose response in preventing recurrent cardiovascular events, and to determine if a dose lower than 150 mg would have a favorable risk benefit ratio. This was in agreement with Health Authority feedback concerning the potential inability to adequately examine canakinumab's dose response in preventing recurrent cardiovascular events when studying the 150 and 300 mg dose only, which may not result in adequate separation of efficacy measurements and lack of data on doses less than 150 mg quarterly, which may have a favorable safety profile.

Amendment 6 also increased the sample size to 17,200 patients in order to have the power of having at least one dose significant of ≥ 90% and to also have ≥ 80% power for the 50 and 150 mg doses individually when assuming that all doses have a 20% relative risk reduction. Following this amendment, randomized allocation to the four trial arms will be unbalanced in order to optimize power, now that three active arms are compared versus a common control arm. Overall across both trial parts an approximately 1.5:1:1:1 (placebo: 50 mg canakinumab: 150 mg canakinumab: 300 mg canakinumab) allocation is targeted.

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Amendment 6 also clarified the documentation requirements for spontaneous MI inclusion criteria, women of child-bearing potential exclusion criteria and tuberculosis exclusion criteria. This amendment included an age-related macular degeneration case report form to collect data on exploratory hypothesis that canakinumab may impact incidence of age-related macular degeneration and additionally specified that blood for biomarkers would be collected on an annual basis at selected sites. The analysis plan was updated to insert the evaluation of the 50 mg dose into the pre-specified closed testing procedure for primary and key secondary endpoints.

Amendment 5

Short summary of the amendment rationale and major changes

In order to comply with the European Competent Authorities request in the context of the Voluntary Harmonization Procedure (VHP), additional information regarding potential early study termination was added to Section 5.5.1.

Amendment 4

Short summary of the amendment rationale and major changes

In order to comply with a Health Authority (PMDA) request from Japan, additional instruction for reporting of specific pre-defined endpoints in Japan was added. This instruction applies to Japan only. Section 7.2 describes the specific pre-defined endpoints in Japan that require expedited reporting to Novartis Pharma K.K.

Amendment 3

Short summary of the amendment rationale and major changes

In amendment 1 an early high dose regimen was selected for both the 150 mg and 300 mg arms whereby each of these doses would be administered twice, over two week period, at randomization (month 0) and at week 2 (month 0.5). To provide a greater separation between the active-dose arms, the early high dose regimen in the 150 mg arm has been removed. This is in agreement with health authority feedback.

An exploratory objective has been added to examine the impact of the early high dose regimen between 300 mg arm (with the early high dose administered) and the 150 mg arm (with no early high dose administered) on clinical cardiovascular events.

To maintain the integrity of the study the data from the interim analyses of T2DM related glycemic control parameters will not be shared with Novartis management as noted in Section 3.5. This is compliant with health authority feedback.

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Amendment 2

Short summary of the amendment rationale and major changes

In the original protocol all deaths, cardiovascular and non-cardiovascular, were reported as potential endpoints and were adjudicated by cardiovascular clinical adjudication committee. Only those deaths, which the adjudication committee determined to be non-cardiovascular deaths, were reported as SAEs after adjudication was completed.

In order to comply with the recent 21 CFR Parts 312 and 320 regulation and draft FDA guidance on Safety Reporting Requirements for INDs and BE/BA Studies, section on reporting clinical endpoints (21 CFR 312.32 (c)(5)), protocol section 7.2 has been revised to assure that certain selective study drug related non-cardiovascular deaths will be reported both as study endpoints and SAEs as soon as study site has been notified of such events without waiting for adjudication committee to complete the adjudication process. This revised SAE reporting procedure fulfills requirements in the above mentioned regulation and draft FDA guidance.

In addition, the definition of pre-diabetes was revised to include impaired fasting glucose, FPG 100-125 mg/dL (5.6-6.9 mmol/L), as a criterion together with the original criterion of HbA1c 5.7-6.4% based on FDA feedback on IND filing of this protocol.

Amendment 1

Short summary of the amendment rationale and major changes

In the original protocol, the dose of canakinumab that provided near maximal biomarker suppression was selected as 150 mg quarterly, and an additional lower dose was selected below this level at 50 mg quarterly. However, as more efficacy data has been analyzed and safety data has accumulated for canakinumab in rheumatoid arthritis and gout patients, safety across a wide range of doses has continued to show a well tolerated and safe profile following higher dose administration. Thus the opportunity has arisen for the CACZ885M2301 protocol to evaluate a higher canakinumab dose since the dose needed for adequate IL-1β neutralization within the plaque or systemically in inflammation-based atherosclerosis is not established. Therefore, a higher dose might deliver greater efficacy than originally selected doses. Thus, as indicated here prior to randomization of any trial participants, the doses to be evaluated in CACZ885M2301 will be placebo s.c. quarterly, 150 mg canakinumab s.c. quarterly and 300 mg canakinumab s.c. quarterly. In addition, currently available safety data provides the opportunity to introduce an early higher dose administration in order to achieve early anti-inflammatory benefit in this high risk cardiovascular population. This induction period provides drug administration twice over a 2 week period and seeks to achieve optimal IL-1β suppression early to provide optimal clinical benefit. Thus, the CACZ885M2301 trial regimens will consist of:

(a) placebo s.c. at randomization (month 0), placebo s.c. at week 2 (month 0.5), placebo s.c. at week 12 (month 3), and then placebo s.c. quarterly;

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(b) canakinumab 150 mg s.c. at randomization (month 0), canakinumab 150 mg s.c. at week 2 (month 0.5), canakinumab 150 mg s.c. at week 12 (month 3), and then canakinumab 150 mg s.c. quarterly; and

(c) canakinumab 300 mg s.c. at randomization (month 0), canakinumab 300 mg s.c. at week 2 (month 0.5), canakinumab 300 mg s.c. at week 12 (month 3), and then canakinumab 300 mg s.c. quarterly.

Advantages of a 300 mg quarterly dose rather than the 50 mg quarterly dose and an additional early dose of canakinumab (either 150 mg or 300 mg) are supported by data that de-couples the biomarker dose effect from gene expression dose effect. The proposed dose regimens are aimed to provide optimal suppression of potential auto-induction of IL-1β and greater early suppression of IL-1β related gene expression. IL-1β auto-induction has been shown in human mononuclear blood, vascular endothelial and vascular smooth muscle cells in vitro and in rabbits in vivo where IL-1 has been shown to induce its own gene expression and circulating IL-1β level (Dinarello et al. 1987, Warner et al. 1987a, and Warner et al. 1987b). These studies suggested that IL-1 induced IL-1 gene expression may provide a positive feedback mechanism in the pathogenesis of atherosclerosis and promote atherosclerosis. This consequently suggests that suppression this feedback mechanism may provide benefits in the atherosclerotic lesion. To accommodate this change in administration of canakinumab, a week 2 visit for drug administration and safety assessments was added to the study visit schedule. The change in dosing regimen necessitated an update to the definition of the safety set. The safety set definition was based on the new Novartis Cardiovascular Clinical Science Unit standards. Similarly, the definition of the censoring date was aligned with these standards. This definition reflects that if there was contact with a patient without the patient attending a visit, then the visit date – in the absence of other information – should be the date of the last contact with the patient.

In addition, the following errors and omissions in the original protocol were corrected:

- Pharmacogenomics information was added to the protocol and study visit schedule
- Troponin I and creatinine kinase MB fraction were added for patients with elevated total creatinine kinase
- Genetics sample storage will be at the Central Laboratory
- SAE reporting instructions were corrected to direct investigators to follow instructions provided in the investigator folder
- Supraventricular tachycardia and atrial fibrillation definitions were added to the protocol
- CABG-MI definition was updated to follow universal MI definition (Thygesen et al 2007)
- Diabetes related definitions used in stratification section were updated
- PK/PD/IG sampling time-points were updated
- HOMA calculation was removed
- A confirmation of elevated ALT/AST and total bilirubin is no longer required at screening

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Protocol synopsis

Title of study: A randomized, double-blind, placebo-controlled, event-driven trial of quarterly subcutaneous canakinumab in the prevention of recurrent cardiovascular events among stable post-myocardial infarction patients with elevated hsCRP

Purpose and rationale: The purpose of this trial is to test the hypothesis that canakinumab treatment of patients with MI at least one month prior to study entry and elevated hsCRP will prevent recurrent cardiovascular events. A secondary hypothesis, that canakinumab treatment in patients with MI and prediabetes, will prevent new onset diabetes (NOD) will also be tested. The trial is pivotal for registration for canakinumab for cardiovascular risk reduction. An optional extension to the study will be conducted following the completion of the pivotal phase with the purpose to further characterize long-term safety on continued exposure to canakinumab in trial participants.

Objectives:

Primary Objective

The primary objective of this clinical trial is to demonstrate the superiority of at least one dose of canakinumab compared to placebo in reducing the risk of recurrent major cardiovascular disease events (cardiovascular death, non-fatal MI and stroke) in a population of clinically stable post-MI patients with elevated hsCRP receiving standard of care.

Key and other secondary objectives

- To demonstrate superiority of canakinumab compared to placebo on the composite endpoint of CV death, non-fatal MI, stroke, and hospitalization for unstable angina requiring unplanned revascularizations.
- To demonstrate superiority of canakinumab compared to placebo on the endpoint of new onset type 2 diabetes among those with pre-diabetes at randomization
- To demonstrate superiority of canakinumab compared to placebo on the composite endpoint of all-cause mortality, non-fatal MI and stroke.
- To demonstrate superiority of canakinumab as compared to placebo on the endpoint of all-cause mortality
- To evaluate the long-term safety of canakinumab therapy in a placebo (standard of care)-controlled setting
- Extension: to obtain further follow-up information on long-term safety on continued exposure to canakinumab in trial participants

Exploratory Objectives

- To explore whether canakinumab compared to placebo reduces the risk of other cardiovascular disorders with a known inflammatory component:
    - Composite of deep vein thrombosis/pulmonary embolism
    - Supraventricular tachycardia/atrial fibrillation
    - Stent thrombosis (probable or definite)
    - Hospitalization or prolongation of hospitalization due to heart failure
    - Major coronary events composite (CHD death, non-fatal MI)
    - Total vascular events composite
    - Coronary revascularization procedures (PCI or CABG)
    - Stroke by etiology
- To explore the dose response relationship and the effects of induction dosing in terms of cardiovascular endpoints.
- To explore whether canakinumab compared to placebo reduces nephropathy as assessed by urinary albumin/creatinine ratio in patients with T2DM or pre-diabetes at randomization

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- To explore whether canakinumab compared to placebo improves glycemic control among those with type 2 diabetes
- To explore whether canakinumab compared to placebo affects biomarkers of cardiovascular and diabetes risk, including but not limited to inflammatory biomarkers, glycemic control markers, β-cell function markers
- Study drug washout in prediabetic patients: to assess the durability of any potential antidiabetic effect of canakinumab following washout of study drug.
- To explore whether canakinumab as compared to placebo affects patient reported outcomes of tiredness, physical function and performance function and improves health status as assessed by the EQ-5D Quality of Life (QOL) assessment. Extension: To explore whether a QoL effect measured by EQ-5D of canakinumab persists and explore the impact of treatment switch on QoL.
- To explore whether canakinumab as compared to placebo improves age-related macular degeneration
- To perform exploratory pharmacogenetic and pharmacogenomic assessments to examine whether individual genetic variation in genes relating to drug metabolism, major cardiovascular events, type 2 diabetes, and the drug target pathway confer differential response to canakinumab.

Population: Participants eligible for this trial will include male and non-child-bearing potential female patients age 18 years and older who (a) have suffered a documented acute myocardial infarction at least 30 days before randomization and (b) have evidence of systemic inflammation on the basis of a hsCRP $\geq$ 2 mg/L despite the use of standard of care post-MI medical therapies. Standard of care post-MI background therapy includes, but is not limited to, lipid lowering, anti-hypertensive, beta blockers, and anti-platelet therapy as appropriate.

The pivotal phase will be an event-driven global trial conducted in the outpatient setting. It is anticipated that approximately 1,400 cardiovascular endpoints will accrue during the course of the trial (see Section 9.7 for Power Calculations). To accomplish this goal, it is expected that approximately 17,000 patients will need to be screened in order to randomize approximately 10,000 patients. All participants of the pivotal phase who continue to be eligible to receive study drug will be offered the option to enter the extension phase.

Key Inclusion/Exclusion criteria:

Inclusion

Patients eligible for inclusion in this study must fulfill all of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Male, or Female of non-child-bearing potential
3. Age ≥ 18 years at Visit 1.
4. Documented spontaneous MI (diagnosed according to the universal MI criteria with or without evidence of ST segment elevation) at least 30 days before randomization. (Thygesen et al 2007)
   - Diagnosis of the qualifying MI should be based on medical history of clinical symptoms consistent with myocardial ischemia associated with elevation of cardiac biomarkers above the 99th percentile of the upper reference limit (preferably troponin) OR development of new pathological Q waves regardless of symptoms. For details, refer to the Universal Definition of MI (Thygesen et al 2007).
   - Please see below for documentation requirements.
     a. Acute MI (hospitalization records): requires documentation of a rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th

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percentile of the upper reference limit (URL) or above criteria diagnostic for MI AND evidence of myocardial ischemia as demonstrated by at least one of the following :

i. Symptoms of ischemia
ii. ECG changes indicative of new ischemia (new ST-T changes or new LBBB)
iii. Development of pathologic Q waves (please see appendix 3 for definitions of pathological Q waves)
iv. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

b. Prior MI (no hospital records for acute event available): requires documentation of any one of the following :

i. Development of pathological Q waves with or without symptoms (please see appendix 3 for definitions of pathological Q waves)
ii. Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause
iii. Pathologic findings of a healed or healing MI

- Patients with MI resulting from PCI or CABG will not be eligible

5. Have an hsCRP ≥ 2 mg/L at screening (Visit 1) (collected less than 60 days prior to Visit 2 and performed at the central laboratory, which is a minimum of 28 days after qualifying MI or after any PCI performed separately from qualifying MI) on stable (at least 4 weeks) long-term (cardiovascular) medications.

Exclusion

Patients fulfilling any of the following criteria are not eligible for inclusion in this trial:

1. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test
2. Women of child-bearing potential defined as all women physiologically capable of becoming pregnant, UNLESS they are
   - Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone or partial or total hysterectomy, only when the reproductive status of the woman has been confirmed by follow up hormonal level assessment is she considered not of child bearing potential

     [For Croatia only]

     [In Croatia, women who are < 50 years of age must have >2 years of amenorrhea or minimum of 1 year of amenorrhea with FSH levels of ≥40 IU determined on 2 or more occasions at least one month apart]
3. Any of the following concomitant diseases
   - Planned coronary revascularization (PCI or CABG) or any other major surgical procedure
   - Major non-cardiac surgical or major endoscopic procedure within the past 6 months prior to Visit 1
   - Multi-vessel CABG surgery within the past 3 years
   - Symptomatic patients with Class IV heart failure (HF) (New York Heart Association [NYHA])
   - Uncontrolled hypertension (defined as an average SBP >160 mmHg or an average diastolic blood pressure (DBP) >100 mmHg at Visit 1. Patients are allowed to be re-evaluated, at the discretion of investigator for this criterion if anti-hypertensive therapy has been started or increased as a result of initial screening blood pressure above these limits. (Mancia et al 2009).

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- Uncontrolled diabetes as defined by the investigator
- Nephrotic syndrome or eGFR < 30 mL/min/1.73 m^2 per MDRD formula or kidney transplant (regardless of renal function), at Visit 1
- Known active or recurrent hepatic disorder (including cirrhosis, hepatitis B and hepatitis C (positive or indeterminate central laboratory results), or ALT/AST levels > 3 times ULN or total bilirubin > 2 times ULN), Visit 1
- Prior malignancy other than basal cell skin carcinoma

4. A history of alcohol and/or substance abuse that could interfere with the conduct of the trial
5. History or evidence of tuberculosis (TB) (active or latent) infection or one of the risk factors for TB such as but not limited or exclusive to:
   a. History of any of the following: residence in a congregate setting (e.g. jail or prison, homeless shelter, or chronic care facility), substance abuse (e.g. injection or non-injection), health-care workers with unprotected exposure to patients who are at high risk of TB or patients with TB disease before the identification and correct airborne precautions of the patient
   b. Close contact (i.e. share the same air space in a household or other enclosed environment for a prolonged period (days or weeks, not minutes or hours)) with a person with active pulmonary TB disease within the last 12 months.
   c. Evidence of TB (active or latent) infection, at Visit 1, determined by purified protein derivative (PPD) skin test and/or QuantiFERON®-TB Gold (QFT-g) assay as defined by country guidelines.
      i. If presence of TB (active or latent) is established, then treatment (according to country guidelines for TB treatment or TB treatment with immunomodulating drugs) must have been initiated or completed prior to randomization per country guidelines.
      ii. In the absence of country TB (active or latent) guidelines, the following has been demonstrated: TB has been treated adequately with antibiotics, cure can be demonstrated, and risk factors resulting in TB exposure and contracting TB have been removed (e.g. the patient does not live anymore in high TB exposure setting).
6. History of ongoing, chronic or recurrent infectious disease
7. Patients with suspected or proven immunocompromised state, including (a) those with evidence of Human Immunodeficiency Virus (HIV) infection; Patients on anti-retroviral therapy are excluded (b) those with any other medical condition which in the opinion of the investigator places the patient at unacceptable risk for participation in immunomodulatory therapy; or (c) those requiring systemic or local treatment with any immune modulating agent in doses with systemic effects e.g. high dose oral or intravenous steroids (> 20 mg prednisone orally daily for > 14 days, > 5 mg prednisone orally daily or equivalent dose of intravenous steroid) or high dose methotrexate (> 15 mg weekly). Topical, inhaled, local steroid use in doses that are not considered to cause systemic effects are permitted.
8. Live vaccinations within 3 months prior to the randomization visit or live vaccinations planned during the trial.
9. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.
10. Patients who have received an investigational drug or device within 30 days (inclusive) of Visit 1, or who are expected to participate in any other investigational drug or device study during the conduct of this trial, except for patients who have an investigational drug eluting stent (DES), provided that they have completed the DES trial. FDA/country-specific drug regulatory authority approved DES devices are permitted.
11. Any biologic drugs targeting the immune system (for example, TNF blockers, anakinra, rituximab, abatacept, tocilizumab)
12. Any life threatening condition with life expectancy < 5 years, other than vascular disease that might prevent the patient from completing the study

Investigational and reference therapy:

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Following protocol amendment 6 (trial part 2) patients will be assigned to one of the following 4 treatment arms in a ratio of 1.3 : 1.3 : 1.4 : 2

- Canakinumab 300 mg s.c. at randomization, 300 mg s.c. at week 2, 300 mg s.c. at week 12, and thereafter 300 mg s.c. quarterly
- Canakinumab 150 mg s.c. at randomization, placebo s.c. at week 2, 150 mg s.c. at week 12, and thereafter 150 mg s.c. quarterly
- Canakinumab 50 mg s.c. at randomization, placebo s.c. at week 2, 50 mg s.c. at week 12, and thereafter 50 mg s.c. quarterly
- Placebo s.c. at randomization, at week 2, at week 12, and thereafter quarterly

Prior to protocol amendment 6 (trial part 1) patients were assigned to one of the following 3 treatment arms in a ratio of 1:1:1

- Canakinumab 150 mg s.c. at randomization, placebo s.c. at week 2, 150 mg s.c. at week 12, and thereafter 150 mg s.c. quarterly
- Canakinumab 300 mg s.c. at randomization, 300 mg s.c. at week 2, 300 mg s.c. at week 12, and thereafter 300 mg s.c. quarterly
- Placebo s.c. at randomization, at week 2, at week 12, and thereafter quarterly

Across trial parts 1 and 2 this is expected to approximately result in a 1:1:1:1.5 allocation.

For patients who are unable to tolerate the protocol-specified dosing intervals, dose interruptions are permitted in order to keep the patient on study drug. Patients are encouraged to continue study medication; however; they are allowed to interrupt and restart medication at any time during the study at the discretion of the investigator.

For the extension phase, all participants except for prediabetic patients will remain on their pivotal phase assigned treatment arm for the first three extension phase visits (Month 0 to Month 6). After the database from the pivotal study is locked they will be switched to an open-label dose of 150 mg canakinumab at the fourth scheduled extension visit (visit Month 9) (Figure 3-2). The 150 mg dose will be administered until the final dose of canakinumab is implemented at the study sites based on the results from the pivotal phase. In contrast to all other participants of the pivotal phase, patients with both randomization and pivotal phase EOS prediabetes will enter a 6-month study drug washout at the beginning of the extension phase by skipping two doses of their pivotal phase blinded assigned treatment arm. At their first visit of the subsequent main drug dispensing period of the extension (visit Month 0) they will receive one dose of their assigned pivotal phase blinded treatment arm before they switch to the open-label dose of 150 mg canakinumab at their next visit (visit Month 3) (Figure 3-3).

Study design: The study is a Phase 3 multi-center, randomized, parallel group, placebo-controlled, double-blind event-driven global clinical trial to evaluate the benefit of quarterly subcutaneous canakinumab doses compared to placebo among stable post-MI patients receiving standard of care therapy who have been selected for an elevated inflammatory burden as determined by hsCRP $\geq$ 2 mg/L. The index qualifying MI must have occurred at least 30 days prior to randomization. Standard of care post-MI background therapy includes but is not limited to appropriate lipid lowering, anti-hypertensive, beta blockers, and anti-platelet therapy as defined by local guidelines. The study is composed of a pivotal phase and an extension phase. The pivotal phase is composed of the screening period and the double blind treatment period. The extension phase is composed of the study drug washout period in prediabetic patients and the main drug dispensing period. PreScreening/Screening will take place no earlier than 28 days after the index MI and on stable (at least 4 weeks) long term medication. Evaluations will include hsCRP and determination of tuberculosis status among other measurements and procedures. After screening visit, patients may be randomized, as soon as, results from screening laboratory and other studies are available. However, this can be no earlier than 30 days after the index MI. For patients who underwent PCI at different hospital admission than the qualifying MI; screening can be initiated no earlier than 28 days following this procedure. For patients who have history of CABG; screening can be initiated no earlier than 3 years after the procedure regardless of timing of the qualifying MI.

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Randomization will be stratified by time since most recent index myocardial infarction (30 days to <6 months and ≥6 months). Recruitment will target approximately 50% of randomized patients with index MI 30 days to 12 months prior to randomization and 50% of randomized patients with index MI > 12 months prior to randomization. The Steering Committee and Sponsor will monitor the patient profiles during recruitment phase and may increase or restrict enrollment of certain sub-groups of patients to avoid imbalances. There will be no upper limit for post MI for inclusion into the trial. The trial is event driven and designed to complete when a total of 1,400 patients have experienced a primary cardiovascular endpoint. Double blind treatment will be continued until the target number of primary cardiovascular endpoints has been reached. Sites will then be notified to have all patients return to complete a pivotal phase EOS visit. The elapsed calendar time to reach conclusion of the study is estimated to be approximately 6 years of treatment and follow-up from the start of enrollment in the trial to the occurrence of 1,400 confirmed adjudicated cardiovascular events.

Interim analyses (IA) of efficacy, futility and safety will be carried out during the study in order to avoid exposing study patients to ineffective treatment or undue risks or to allow study discontinuation in case of overwhelming efficacy. Two interim analyses of efficacy will be performed when approximately 50% of the target number of patients with primary endpoints have been accumulated and the second one when approximately 75% of the planned number of patients with primary endpoints are available. A futility analysis may be performed earlier than the first planned efficacy IA (at approximately 50% primary events) but only after a sufficient number of primary events are accrued, i.e., >25%.

Following the completion of the pivotal phase, every patient who continues to be eligible to receive study drug will be offered the option to continue study drug treatment during the extension phase. The objective of the extension phase is to further characterize long-term safety on continued exposure to canakinumab in trial participants. Consenting patients will be scheduled for visits to dispense study drug and to collect safety data at 3-month intervals. All participants except for prediabetic patients will remain on their pivotal phase assigned treatment arm for the first three extension phase visits (Month 0 to Month 6). After the database from the pivotal study is locked they will be switched to an open-label dose of 150 mg canakinumab at the fourth scheduled extension visit (visit Month 9) (Figure 3-2). The final canakinumab dose will be based on the results from the pivotal phase. The transition to an intermediate dose of 150 mg will avoid further placebo treatment until the final dose of canakinumab is implemented at the study sites. In contrast to all other participants of the pivotal phase, patients with both randomization and pivotal phase EOS prediabetes will enter a 6-month study drug washout at the beginning of the extension phase by skipping two doses of their pivotal phase blinded assigned treatment arm. At their first visit of the subsequent main drug dispensing period of the extension (visit Month 0) they will receive one dose of their assigned pivotal phase blinded treatment arm before they switch to the open-label dose of 150 mg canakinumab at their next visit (visit Month 3) (Figure 3-3). The purpose of the study drug washout in prediabetic patients is to assess to what extent a potential lower incidence of diabetes diagnoses observed on canakinumab relative to placebo treatment during double-blind treatment is explained by a true delay in progression to diabetes as opposed to a lowering of FPG and HbA1c that masks diabetes but does not persist after the washout. The extension phase will collect all safety events (serious and non-serious AEs) including malignancies, infections and major cardiovascular adverse events that were defined as the primary endpoint of the pivotal phase. No adjudication of events will be performed, neither for CV events nor serious infections or malignancies during the extension phase. The extension phase will continue in an individual country for a minimum of two years from the date of the first patients enrolled in that country. The maximum duration of the extension phase will be 2.5 years from the date of the first patient enrolled in that country or until marketed product is available in that country, whichever comes first. While the extension phase is then deemed complete the safety follow-up is anticipated to be continued in registries following study results and discussion with Health Authorities.

Efficacy assessments:

Primary efficacy assessment:

The primary endpoint is defined as the time to the first event of a major cardiovascular event (MACE) occurring during the double-blind treatment period, which is a composite of CV death, non-fatal MI,

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and stroke. An independent adjudication committee that is blinded to treatment assignments will review and adjudicate all clinical events that constitute the composite endpoint.

Key secondary efficacy assessments:

Key secondary efficacy assessments will comprise:

- Time to first event of a composite cardiovascular endpoint consisting of the primary endpoint, and hospitalization for unstable angina requiring unplanned revascularization
- Time to new onset type 2 diabetes among those with pre-diabetes at randomization (time to NOD)

Other secondary efficacy assessments:

Other secondary efficacy assessments will comprise

- Time to first event of, non-fatal MI, stroke and all-cause mortality composite
- Time to all-cause mortality

Exploratory efficacy assessments

Exploratory efficacy assessments are described in (Section 6.4.2) of the clinical study protocol.

Safety Assessments*:*

- Laboratory evaluations
- Height, weight and waist circumference
- Adverse events and serious adverse events, including cardiovascular events, malignancies, and infections
- Discontinuation due to AEs
- Hypoglycemia events
- Injection site reactions
- Physical Examination
- Biomarkers
- Vital Signs
- ECG

Serious allergies/immunological events, serious infections, and malignancies adverse events will be monitored carefully during this trial because these adverse events represent hypothetical mechanism of action related risks of canakinumab therapy.

The extension phase will collect all safety events (serious and non-serious AEs) including malignancies, infections and major cardiovascular adverse events that were defined as the primary endpoint of the pivotal phase. No adjudication of events will be performed, neither for CV events nor serious infections or malignancies.

Other Assessments:

- Assessment of Glycemic Control for T2DM
- Stroke Functional Assessment Sub-Study
- The Modified Rankin Scale, MFSI-SF, SIS-16, EQ-5D,SF-36 Health State Classification, Visual Analogue Scale ‘Thermometer’
- Pharmacokinetics, pharmacodynamics, immunogenicity, pharmacogenetics, pharmacogenomics, and other biomarkers
- Macular Degeneration
- Extension: any potential antidiabetic effect in prediabetic patients following washout of study drug

Data analysis:

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The primary statistical hypotheses are:

- H_{11}: The hazard rate of first adjudication committee confirmed MACE in the canakinumab 300 mg dose group is greater than or equal to that in the placebo group
- H_{21}: The hazard rate of first adjudication committee confirmed MACE in the canakinumab 150 mg dose group is greater than or equal to that in the placebo group
- H_{31}: The hazard rate of first adjudication committee confirmed MACE in the canakinumab 50 mg dose group is greater than or equal to that in the placebo group

Each tested versus the one-sided alternative that the hazard rate is smaller for the respective active dose group than in the placebo group.

These hypotheses will be tested by comparing each dose to placebo with a log-rank test stratified by time since index MI and by trial part using exact method for handling ties on the FAS according to the intent-to-treat principle. The family-wise error rate will be controlled at the two interim analyses and the final analysis using a closed testing procedure that initially assigns all the available significance level to the primary null hypotheses relating to the three doses. Key secondary endpoints for a dose are only tested after the rejection of the primary null hypothesis for that dose.

A fixed Bonferroni split of the one sided alpha will be used to account for the two efficacy interim analyses and the final analysis, with a significance level of 0.01% for the first efficacy interim analysis, 0.04% for the second efficacy interim analysis and 2.45% for the final analysis. In this fashion the family-wise type I error rate will be controlled at the one-sided 2.5% level. This constitutes an equivalent level of evidence as the two-sided 5% level and two-sided p-values will also be reported.

The hazard ratios and their associated confidence intervals will be estimated by means of a Cox proportional-hazards model stratified by time since index MI (< 6 months, ≥ 6 months) and by trial part using treatment (canakinumab doses and placebo) as a factor in the model using exact method for handling ties. Kaplan-Meier type plots will be presented overall and separately by trial part to summarize the time to first event in the composite endpoint, by presenting the time-dependent cumulative frequency and percentage of patients who reach the primary composite endpoint by treatment group.

The components of the composite primary efficacy endpoint (CV death, fatal or non-fatal MI, fatal or stroke) will also be analyzed individually in order to evaluate their contributions to the overall treatment effect.

Based on the FAS, all key secondary efficacy variables will be analyzed with a log-rank test stratified by time since index MI and by trial part, and displayed by means of Kaplan-Meier type plots according to treatment overall and by trial part.

The secondary efficacy variable corresponding to new onset type 2 diabetes in patients with pre-diabetes at randomization will be the time from randomization to the first occurrence of repeated FPG ≥ 126 mg/dL (≥ 7.0 mmol/L) or of a repeated HbA1c $\geq$ 6.5% or of the start of new anti-diabetic medication. Due to the discrete nature of the time points when new onset of type 2 diabetes can be determined, events identified at the same visit time point for different patients will be considered as tied events and exact method for handling ties will be used.

Exploratory time-to-event outcomes will be analyzed using Cox regression models including treatment with time since index MI and trial part as a stratification variable, along with Kaplan-Meier type plots. Exploratory continuous outcome variables (i.e. change from baseline of HbA1c, biomarkers, and patient reported outcomes, etc.) will be analyzed using both a repeated measures analysis of covariance adjusted for baseline value, as well as descriptively.

Safety

The incidence of adverse events (new or worsened) will be summarized by primary system organ class (SOC), preferred term, severity and relationship to study drug. The incidence of death, SAEs, and AEs leading to discontinuation will be summarized separately by primary system organ class and preferred term. Selected SAEs will be narrated.

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The incidence of adverse events related to cardiovascular events in constellations relevant for a description of safety and death, as well as serious infections and malignancy will be specifically investigated. Appropriate time to event assessments will be used if warranted.

Laboratory data will be summarized by shift tables and categorical analyses using extended normal ranges if thresholds of interest are identified based on baseline to most extreme post-baseline value, with summary statistics of raw and change from baseline by visits. Furthermore, notable values will be flagged in data listings.

From the extension phase, the incidence of adverse events (new or worsening) will be summarized by primary system organ class (SOC), preferred term, severity and relationship to study drug. SAEs and AEs leading to discontinuation will be summarized separately by primary system organ class and preferred term. The incidence of death will be summarized by the primary cause.

Sample Size Calculation

With a sample size of approximately 10,000 randomized patients and assigned in a 1:1:1 allocation ratio to canakinumab 150 mg, canakinumab 300 mg, and placebo in trial part 1 and in a 2 : 1.4 : 1.3 : 1.3 allocation ratio to placebo, canakinumab 50 mg, canakinumab 150 mg, and canakinumab 300 mg in trial part 2, it is expected that 1,400 patients will experience a primary endpoint approximately 6 years after study initiation. 1,400 endpoints are necessary to achieve a power ≥ 90% to demonstrate the superiority of at least one dose of canakinumab compared to placebo on the primary endpoint assuming a relative hazard reduction of 20% for all active doses and to also have ≥ 80% power for the 50 and 150 mg doses individually.

No sample size calculation was performed for the extension phase, because the key objective of the extension phase is long-term safety assessment in participants of the pivotal phase.

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1 Introduction

1.1 Background

Atherosclerosis is a disease characterized by chronically high inflammatory state. Arterial inflammation and endothelial dysfunction play key roles at all stages of the atherothrombotic process. Inflammatory mediators are intimately implicated with the cascade of events leading to atherosclerotic plaque initiation, progression and rupture. Vascular endothelial cells express a variety of adhesion molecules that recruit monocytes when chronically exposed to noxious stimuli or pathological conditions. Adverse conditions such as hyperlipidemia are associated with enrichment of a pro-inflammatory subset of monocytes. These monocytes apparently enter the intima under the influence of chemotactic stimuli and engulf modified low density lipoprotein (LDL) and cholesterol crystals (Duewell et al 2010). The material internalized by phagocytes induces phagolysosomal damage and subsequent leakage of contents into cytosol to activate inflammasomes and caspase 1, and consequently the generation of interleukin-1b (IL-1β) from pro-interleukin-1β.

Interleukins are key mediators in the chronic vascular inflammatory response in cardiovascular (CV) disease and have been demonstrated in animal models and in humans to be potent modulators of pro-inflammatory processes. The fact that these cytokines and their receptors are highly expressed and are functional in almost all cell types implicated in the pathogenesis of atherosclerosis including smooth muscle cells, certain subset of macrophages and T cells as well as endothelium support the role of interleukins in vascular disease. For example, IL-1β is a potent smooth muscle cell mitogen, an activator of endothelial cells and increases extra cellular matrix and collagen deposition, which plays a role in plaque burden and arterial thickening. Furthermore, lack of IL-1β or ablation of IL-1 receptor has been shown to decrease severity of atherosclerosis in apoE deficient mice. Thus, antagonism of the IL-1β mediated inflammation is a primary and attractive target for ameliorating the vessel wall inflammation associated with atherosclerosis.

Canakinumab (ACZ885) is a fully human monoclonal anti-human IL-1β antibody of the IgG1/k isotype, being developed for the treatment of IL-1β driven inflammatory diseases. It is designed to bind to human IL-1β and thus blocks the interaction of this cytokine with its receptors. The antagonism of the IL-1β mediated inflammation using canakinumab in lowering high sensitivity C-reactive protein (hs-CRP) and other inflammatory marker levels has shown an acute phase response in patients with Cryopyrin-Associated Periodic Syndrome (CAPS) and rheumatoid arthritis (data on file). This evidence has been replicated in patients with type 2 diabetes mellitus (T2DM) using canakinumab (data on file), and with other IL-1β antibody therapies in development.

Therefore, canakinumab is expected to reduce the risk of future occurrence of major cardiovascular events in patients with recent past myocardial infarction (MI) by preventing IL-1β mediated vascular wall inflammation and endothelial dysfunction.

Atherosclerotic vascular disease is the primary cause of morbidity and mortality in individuals with and without T2DM. The progression of atherosclerosis from endothelial dysfunction to vascular occlusion or to plaque rupture is the underlying mechanism responsible for many

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debilitating and life-threatening diseases such as MI, stroke and peripheral vascular disease (PVD). These diseases occur at higher frequency in T2DM patients and continue to increase despite use of current optimal therapies. There is also higher mortality rate after first MI in patients with T2DM compared to those without T2DM. Mortality associated with impaired glucose tolerance is 1.96 times higher compared to normal glucose tolerance. Thus, novel therapies that may improve vascular function, decrease atherosclerotic burden, and translate to a decrease in cardiovascular events would fill a significant unmet medical need.

T2DM is also a disease that is characterized by a high inflammatory state. Pre-clinical data suggests IL-1β is of key importance in the progressive functional impairment and destruction of β-cells in type 2 diabetes. Pancreatic β cells secrete IL-1β in response to elevated glucose exposure promoting further impairment of cellular viability via an autocrine action. IL-1β antagonism inhibits β cell death, promotes β cell proliferation, potentiates β cell glucose-induced insulin secretion and improves insulin sensitivity. Blocking IL-1β activity with an IL-1 receptor antagonist as well as a neutralizing IL-1β antibody in clinical trials reduced glycosylated hemoglobin (HbA1c). Neutralization of IL-1β activity in the pancreatic islets is thus emerging as an attractive target for the treatment and prevention of type 2 diabetes. For T2DM prevention canakinumab's primary direct action is expected to prevent the IL-1β mediated destruction of pancreatic β-cells and thus prevent or delay progression of disease, which to date is a completely unmet need.

Therefore, canakinumab is expected to prevent new onset T2DM in patients with a recent past MI and that are pre-diabetic, and who are at risk of developing T2DM.

As demonstrated in a comprehensive 2010 meta-analysis of 54 prospective cohort studies, the inflammatory biomarker hsCRP is an independent risk factor for future cardiovascular events that (a) has a magnitude of effect similar to or larger than that of blood pressure or cholesterol and (b) has long-term stability and reproducibility at least as good as these widely-accepted risk factors (Kaptoge et al 2010). Abundant clinical trial data further demonstrate that persistent elevations of hsCRP are a major risk factor of recurrent vascular risk following myocardial infarction; for example, as demonstrated in the PROVE IT-TIMI 22 (Ridker et al 2005) and A-to-Z (Morrow et al 2006) trials. In both trials patients with known vascular disease and persistent elevation of hsCRP were at roughly double the risk for recurrent events compared to those with normal hsCRP levels. Further, stratification by hsCRP has proven highly effective in determining populations in who added cardiovascular benefits are observed with the use of efficacious lipid lowering agents, which also possess, anti-inflammatory properties. This has been proven in primary prevention studies as including the AFCAPS/TexCAPS (Ridker et al 2001) and JUPITER trials (Ridker et al 2008, Ridker et al 2009) as well as in the setting of congestive heart failure (CHF) in the CORONA trial where efficacy of intervention was seen only among those with hsCRP $\geq$ 2 mg/L. Indeed, in this latter example, had stratification been done by hsCRP on an a priori basis, the trial would have been reported out as an overwhelming positive rather than as a null finding (McMurray et al 2009)

A direct anti-inflammatory agent could, in theory, be tested at any stage of the atherothrombotic process. However, the most appropriate population to test this hypothesis is one in which (a) patients are known to be at increased risk despite current therapy, and (b) there is biochemical evidence of a persistent heightened inflammatory response despite usual

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care. Recognizing these constraints, a primary prevention population would be infeasible due to the exceptionally large sample size required and because an extremely low side effect profile is typically required in that setting. In contrast, patients who have survived a MI are clinically stable, and who have persistently elevated hsCRP levels despite aggressive treatment are an optimal population in which to undertake a test of the inflammatory hypothesis of atherothrombosis. This population is no longer at risk for plaque rupture due to altered wound healing, yet remains at high risk for recurrent vascular events despite use of all accepted therapies. If alternatively designed to enroll post-MI patients without regard to hsCRP, the proposed trial would substantially lose power and would expose large numbers of individuals with already controlled inflammation to IL-1β inhibition. All of these effects would result in an adverse shift in the benefit to risk ratio as well as greatly increase study costs.

1.2 Purpose

The purpose of this trial is to test the hypothesis that canakinumab treatment of patients with MI at least one month prior to study entry and elevated hsCRP will prevent recurrent cardiovascular events. A secondary hypothesis, that canakinumab treatment in patients with MI and prediabetes, will prevent new onset diabetes (NOD) will also be tested. The trial is pivotal for registration for canakinumab for cardiovascular risk reduction.

The purpose of the extension phase is to collect additional long-term safety data on continued exposure to canakinumab in patients who participated in the pivotal phase.

2 Study objectives

2.1 Primary objective

The primary objective of this clinical trial is to demonstrate the superiority of at least one dose of canakinumab compared to placebo in reducing the risk of recurrent major cardiovascular disease events (cardiovascular death, non-fatal MI and stroke) in a population of clinically stable post-MI patients with elevated hsCRP receiving standard of care.

2.2 Secondary objectives

Key secondary efficacy objectives

- To demonstrate superiority of canakinumab compared to placebo on the composite endpoint of CV death, non-fatal MI, stroke, and hospitalization for unstable angina requiring unplanned revascularizations.
- To demonstrate superiority of canakinumab compared to placebo on the endpoint of new onset type 2 diabetes among those with pre-diabetes at randomization

Other secondary efficacy objectives

- To demonstrate superiority of canakinumab compared to placebo on the composite endpoint of all-cause mortality, non-fatal MI and stroke.

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- To demonstrate superiority of canakinumab as compared to placebo on the endpoint of all-cause mortality

Safety objectives

- To evaluate the long-term safety of canakinumab therapy in a placebo(standard of care) - controlled setting
- Extension phase: to obtain further follow-up information on long-term safety on continued exposure to canakinumab in trial participants

2.3 Exploratory objectives

- To explore whether canakinumab compared to placebo reduces the risk of other cardiovascular disorders with a known inflammatory component:
    - Composite of deep vein thrombosis/pulmonary embolism
    - Supraventricular tachycardia/atrial fibrillation
    - Stent thrombosis (probable or definite)
    - Hospitalization or prolongation of hospitalization for heart failure
    - Cardiovascular death, non-fatal MI, stroke and all-cause mortality composite
    - Major coronary events composite (CHD death, non-fatal MI)
    - Total vascular events composite
    - Coronary revascularization procedures (PCI or coronary artery bypass graft (CABG))
    - Stroke by etiology
- To explore the dose response relationship and the effects of induction dosing in terms of cardiovascular endpoints.
- To explore whether canakinumab compared to placebo reduces nephropathy as assessed by urinary albumin/creatinine ratio in patients with T2DM or pre-diabetes at randomization
- To explore whether canakinumab compared to placebo improves glycemic control among those with type 2 diabetes
- To explore whether canakinumab compared to placebo affects biomarkers of cardiovascular and diabetes risk, including but not limited to inflammatory biomarkers, glycemic control markers, β-cell function markers
- To explore whether canakinumab as compared to placebo affects patient reported outcomes of tiredness, physical function and performance function and improves health status as assessed by the EQ-5D Quality of Life (QOL) assessment. To explore in the extension phase whether a QoL effect measured by EQ-5D of canakinumab persists and explore the impact of treatment switch on QoL
- To explore whether canakinumab as compared to placebo improves age-related macular degeneration
- To perform exploratory pharmacogenetic and pharmacogenomic assessments to examine whether individual genetic variation in genes relating to drug metabolism, major

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cardiovascular events, type 2 diabetes, and the drug target pathway confer differential response to canakinumab.

- Study drug washout in prediabetic patients: to assess the durability of any potential antidiabetic effect of canakinumab following washout of study drug.

3 Investigational plan

3.1 Study design

This study is a Phase 3, multi-center, randomized, parallel group, placebo-controlled, double-blind event-driven global clinical trial. The CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) study is designed to evaluate the benefit of quarterly doses of 50 mg and 150 mg canakinumab and an induction followed by quarterly dose of 300 mg canakinumab subcutaneously compared to placebo in stable post-MI patients receiving standard of care therapy who have been selected by an elevated inflammatory burden as determined by hsCRP $\geq$ 2 mg/L. The index qualifying MI must have occurred at least 30 days prior to randomization. There is no upper limit for post- MI for inclusion into the study. Standard of care post-MI background therapy includes but is not limited to appropriate lipid lowering, anti-hypertensive, beta blockers, and anti-platelet therapy as defined by local guidelines. Patients should also be instructed to follow heart healthy (low fat) diet and regular exercise program.

Pre-Screening: Pre-screening is a key element to successfully identifying the correct patients to be screened for this clinical study. All patients should have an available hsCRP value prior to the time of screening. The available hsCRP value should be at least 28 days after a cardiovascular event or procedure or major surgical procedure, and must be less than 60 calendar days prior to screening (Note: centrally-performed prescreen hsCRP results must be obtained less than 60 calendar days prior to Visit 2 to be used to evaluate Inclusion criterion 5, Section 4.1).

The Pre-screening visit should be used after review of the patient's charts to determine patient's eligibility and to obtain an hsCRP value.

The Pre-screening visit will take place no earlier than:

- 28 days after the index MI and on stable long term medication.
- 28 days after a PCI if it was during a different hospital admission than the qualifying MI. Pre-screening can only be initiated following this procedure.
- 3 years post a Multi-vessel CABG procedure regardless of timing of the qualifying MI

Patients with a prescreen hsCRP $\geq$ 2 mg/L from the central laboratory do not require an hsCRP measurement at Visit 1, provided the prescreen hsCRP blood sample was drawn less than 60 days prior to Visit 2 and the patient is on stable (at least 4 weeks) long term medications. All pre-screened patients must be called into the Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS). Note: The Pre-screening visit should not occur and instead be rescheduled if the patient presents with an acute viral or bacterial infection at the Pre-screen visit.

Screening: Screening will take place no earlier than:

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- 28 days after the index MI and on stable long term medication.
- 28 days after a PCI if it was during a different hospital admission than the qualifying MI. Screening can only be initiated following this procedure.
- 3 years post a Multi-vessel CABG procedure regardless of timing of the qualifying MI.

All screened patients must be called into the IVRS/IWRS. Screening evaluations will include determination of tuberculosis status, other measurements and procedures, and hsCRP measurement in patients who proceeded directly to Visit 1 due to a prior (non-centrally performed) hsCRP, ≥ 2mg/L performed 60 days to prior Visit 1. After the screening visit, patients may be randomized as soon as results from the screening laboratory and other studies are available. However, this can be no earlier than 30 days after the index MI. Note: For patients who require an hsCRP measurement at Visit 1 only, the Screening Visit/Visit 1 should not occur and instead be rescheduled if the patient presents with an acute viral or bacterial infection at Visit 1.

The time between screening and randomization should be approximately 4 weeks with the qualifying centrally-performed hsCRP obtained no less than 60 days prior to Visit 2 (Note: the maximum amount of time between Visit 1 and Visit 2 should not exceed 60 days with the exception of those who initiate treatment for tuberculosis (TB) as described below). Patients may be randomized as soon as eligibility assessments have been completed. Generally rescreening is not allowed. However, patients may be re-evaluated as noted in the inclusion and exclusion sections (applicable for out of range systolic and diastolic blood pressure and patients requiring TB treatment. Note: Patients who initiate treatment for TB and who per country guidelines can be randomized into the trial < 60 days after starting TB treatment, must have a repeat hsCRP performed just prior to randomization which is ≥ 2 mg/L; those who can be randomized into the trial > 60 days after starting TB treatment, must be re-evaluated just prior to randomization for all Inclusion/Exclusion criteria including central laboratory evaluations). Patients re-evaluated will retain their screening number and be randomized or screen failed based upon the result of the re-evaluation.

Randomization: Randomization will be stratified by time since most recent index myocardial infarction (30 days to <6 months and ≥6 months). Recruitment will target approximately 50% of randomized patients with index MI 30 days to 12 months prior to randomization and 50% of randomized patients with index MI > 12 months prior to randomization. Patients should be hemodynamically stable at the time of randomization. The Steering Committee and Sponsor will monitor the patient profiles during recruitment phase and may increase or restrict enrollment of certain sub-groups of patients to avoid imbalances. There will be no upper limit for post MI for inclusion into the trial. Once randomized, patients will return to the clinic for scheduled visits as shown in the study assessment schedule. Some assessments at these visits will include physical examinations, vital sign measurements, electrocardiogram (ECG), instruction on how to follow a heart healthy (low fat) diet and regular exercise program and clinical laboratory measurements including glucose control, lipids, biomarkers, and routine safety assessments.

Patients will have scheduled assessments at months 0.5, 1.5, and 3 after randomization and quarterly visits thereafter to evaluate safety and the occurrence of any trial endpoints, as well as, to receive scheduled (excluding month 1.5) subcutaneous injections of active therapy and/

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or placebo. Genetic blood samples and biomarker samples collected in a subset of patients at randomization, month 3, one year, annually at selected sites and pivotal phase end of study (EOS) visit will be shipped to the Central Laboratory for long term storage. Upon completion of the pivotal phase, these samples will be analyzed for cardiovascular and metabolic biomarkers and genetic analysis, if prior written informed consent is obtained.

The pivotal phase is event driven and designed to complete when a total of 1,400 patients have experienced a primary cardiovascular endpoint. Double blind treatment will be continued until the target number of primary cardiovascular endpoints has been reached. Sites will then be notified to have all patients return to complete an pivotal phase EOS visit. The elapsed calendar time to reach conclusion of the study is estimated to be approximately 6 years of treatment and follow-up from the start of enrollment in the trial to when 1,400 patients have had a confirmed adjudicated cardiovascular event.

Extension phase: At the first visit of the extension phase (visit Month 0), every trial participant who continues to be eligible to receive study drug will be offered the option to continue study drug treatment during the extension phase. Consenting patients will remain at the 3-month intervals between study visits as shown in the study assessment schedule for the extension phase (Table 6-2 and Table 6-3). All patients must be called into the IVRS/IWRS at every visit throughout the extension phase. For all participants except for prediabetic patients the first visit of the extension phase at Month 0 should occur on the same day as the pivotal phase EOS visit. In case the last drug administration of the pivotal phase occurred within 4 weeks before the pivotal phase EOS visit, the study drug administration at the extension phase Month 0 visit will be skipped and the first injection as part of the extension phase will be performed at the Month 3 visit. All participants except for those with prediabetes will remain on their pivotal phase assigned treatment arm for the first three extension phase visits (Month 0 to Month 6). After the database from the pivotal study is locked they will be switched to an open-label dose of 150 mg canakinumab at the fourth extension phase visit (Month 9) (Figure 3-2). The 150 mg dose is predicted to have the highest likelihood of having the most favorable benefit: risk ratio based on biomarker and clinical data from phase II studies in Type 2 diabetics. The final canakinumab dose will be based on the results from the pivotal phase. The transition to an intermediate dose of 150 mg will avoid further placebo treatment until the final dose of canakinumab is implemented at the study sites. In contrast to all other participants of the pivotal phase, patients with both randomization and EOS prediabetes will enter a 6-month study drug washout at the beginning of the extension phase by skipping two doses of their pivotal phase blinded assigned treatment arm. At their first visit of the subsequent main drug dispensing period of the extension (visit Month 0) they will receive one dose of their assigned pivotal phase blinded treatment arm before they switch to the open-label dose of 150 mg canakinumab at their next visit (visit Month 3 (Figure 3-3). The pivotal phase EOS glycemic status will be assessed based on the last HbA1c and fasting plasma glucose (FPG) data available at the EOS visit. For participants of the prediabetes washout, the first visit of the extension at Month 0 should occur on the same day as the End of Prediabetes Washout visit. The extension phase will collect all safety events (serious and non-serious AEs) reported and will no longer adjudicate any pre-specified efficacy or safety events. In addition to safety assessments at every visit, annual vital sign measurements will be performed according to the extension phase assessment schedule. The extension phase will continue in an individual country for a minimum of two years from the date of the first patients enrolled

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in that country. The maximum duration of the extension phase will be 2.5 years from the date of the first patient enrolled in that country or until marketed product is available in that country, whichever comes first. Once study closeout date is determined, the site staff is contacted to have the patients return for their extension phase EOS visit. While the extension phase is then deemed complete the safety follow-up is anticipated to be continued in registries following study results and discussion with Health Authorities.

Patients who discontinue study treatment

Every attempt to determine follow-up status of patients who discontinue study treatment, for a*ny* reason prior to the completion of the trial, must be made unless prohibited by local regulations. It is required that these patients are contacted per study schedule (i.e., every 3 months) to ensure all endpoints (safety and efficacy) are collected and reported. It will be at the discretion of the site staff to determine if these patients will be contacted by phone or attend the regularly scheduled visits.

For patients whose treatment is stopped as a result of a Data Monitoring Committee (DMC) recommendation to suspend treatment in one dose group, follow-up for cardiovascular (CV) and safety events will continue. Since these patients will not receive further study medication, less frequent follow-up will be conducted every 6 months. Continued follow-up will likely enhance understanding of the safety of the other dose groups.

Any patient who stops study treatment, withdraws consent (if re-consented) or becomes no longer lost to follow up, is allowed to restart the study treatment at the discretion of the investigator regardless of length of time off study treatment.

Extension phase: for patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

End of Study Follow-up for all prediabetic patients

Once all study endpoints of the pivotal phase have been reached and the site staff is contacted to have all patients return for their pivotal phase EOS visit, any patient with a prediabetic status at both randomization and at pivotal phase EOS visit (based on last lab results available at the EOS visit), will enter into an additional 6-month washout without study drug treatment by skipping two doses of their pivotal phase blinded assigned treatment arm. At the end of the study drug washout, HbA1c and FPG will be performed along with the other study procedures shown in Table 6-3. If no HbA1c value is available from the End of Prediabetes Washout visit or if a diabetes diagnosis is only based on one FPG value of ≥ 126 mg/dL (≥ 7 mmol/L) from the End of Prediabetes Washout visit, an unscheduled visit should be conducted within 6 weeks. The purpose of this washout period is to assess to what extent a potential lower incidence of diabetes diagnoses observed on canakinumab relative to placebo during pivotal phase double-blind treatment is explained by a true delay in progression to diabetes as opposed to a lowering of FPG and HbA1c that masks diabetes but does not persist after the

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washout. At their first visit of the subsequent main drug dispensing period of the extension (visit Month 0) study drug washout participants will receive one dose of their assigned pivotal phase blinded treatment arm before they switch to the open-label dose of 150 mg canakinumab at their next visit (visit Month 3) (Figure 3-3).

No adjudication of NOD will be performed during the extension phase.

Sub-Studies

All patients who suffer a stroke during the double-blind period of the pivotal phase will participate in the, Post-Stroke Functional Assessment Sub-Study; see Section 6.6.5 for further details.

The CACZ885M2301S1 imaging sub-study (to evaluate the effect of quarterly subcutaneous canakinumab treatment for 24 months versus placebo, on top of standard of care, on the carotid plaque burden measured by vascular MRI in approximately 330 patients) and the CACZ885M2301S2 oral glucose tolerance test sub-study (to determine whether canakinumab compared to placebo, on top of standard of care, increases insulin secretion and insulin sensitivity in approximately 300 patients with type 2 diabetes) were prematurely terminated. The termination was not due to safety or efficacy concerns.

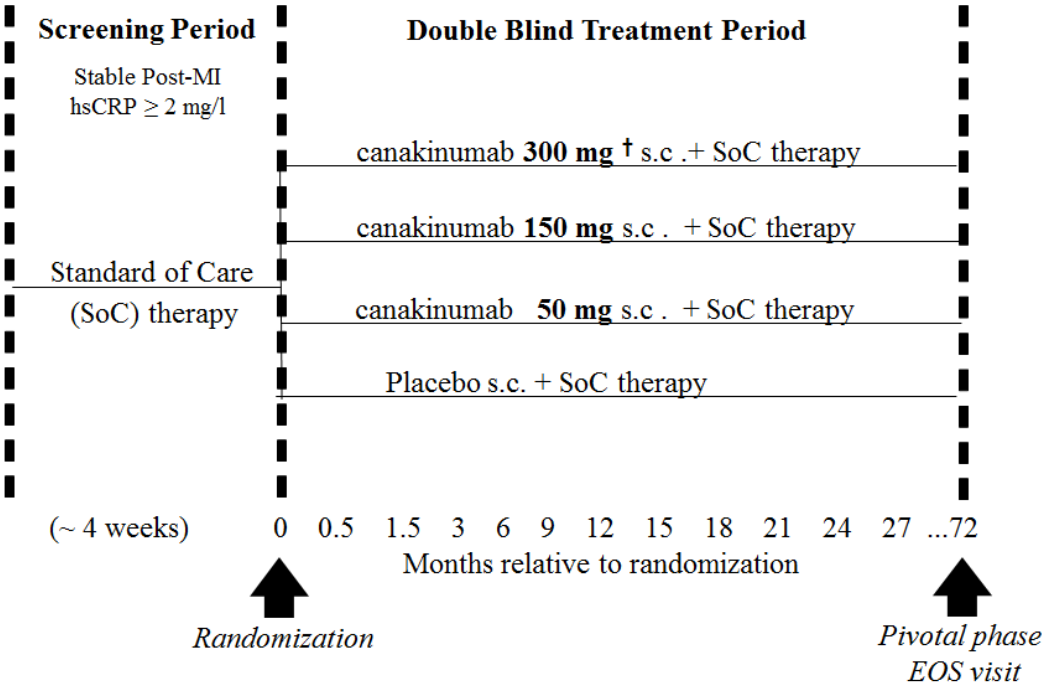
Interim Analysis

Interim analyses will be conducted for this trial; please see Section 3.5 and Section 9.8 for details.

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Figure 3-1 Study design pivotal phase

The pivotal phase is composed of the screening period and the double blind treatment period.

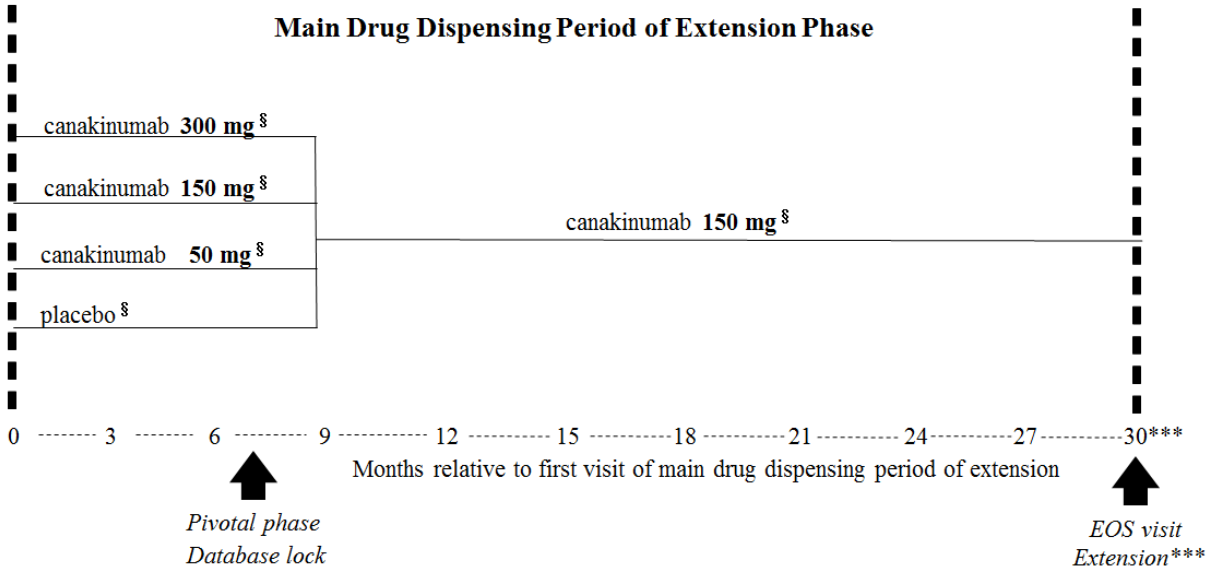


†- canakinumab 300 mg s.c. induction at randomization (month 0) and week 2 (month 0.5), and then 300 mg s.c. quarterly beginning at week 12.

Figure 3-2 Study design of extension phase for patients <u>not</u> participating in study drug washout

For patients not participating in the 6-month study drug washout period, the extension phase is only composed of the main drug dispensing period.

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§plus Standard of Care therapy

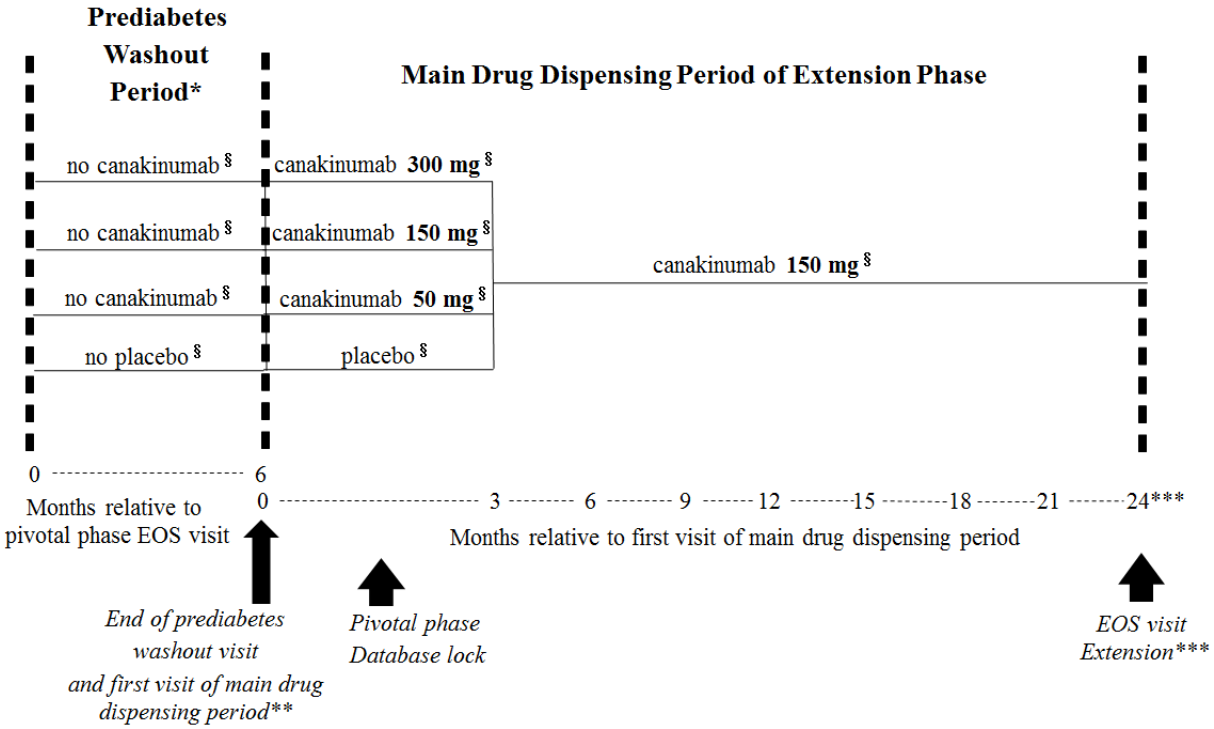
***The extension phase will continue in an individual country for a minimum of two years from the date of the first patients enrolled in that country. The maximum duration of the extension phase will be 2.5 years from the date of the first patient enrolled in that country or until marketed product is available in that country, whichever comes first.

Patients who choose to participate in the extension phase will remain on their pivotal phase blinded assigned treatment arm for the first three extension phase visits (Month 0 to Month 6). After the database from the pivotal study is locked they will be switched to an open-label dose of 150 mg canakinumab at the fourth extension visit (Month 9). The final canakinumab dose will be based on the results from the pivotal phase. The transition to an intermediate dose of 150 mg will avoid further placebo treatment until the final dose of canakinumab is implemented at the study sites.

Figure 3-3 Study design of extension phase for prediabetic patients

For patients with prediabetic status at both randomization and pivotal phase EOS visit the extension phase is composed of the study drug washout period and the main drug dispensing period.

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§plus Standard of Care therapy

*Only patients with prediabetic status from both randomization and pivotal phase EOS visit will enter the study drug washout.

**After the End of Prediabetes Washout visit, the patients will enter the subsequent main drug dispensing period of the extension. The first visit of the main drug dispensing period should occur on the same day as the End of Prediabetes Washout visit.

***The extension phase will continue in an individual country for a minimum of two years from the date of the first patients enrolled in that country. The maximum duration of the extension phase will be 2.5 years from the date of the first patient enrolled in that country or until marketed product is available in that country, whichever comes first.

Prediabetic patients will participate in a 6-month study drug washout at the beginning of the extension phase by skipping two doses of their pivotal phase blinded assigned treatment arm. At their first visit of the subsequent main drug dispensing period of the extension (visit Month 0) study drug washout participants will receive one dose of their assigned pivotal phase blinded treatment arm before they switch to the open-label dose of 150 mg canakinumab at their next visit (visit Month 3, as shown in Figure 3-3).

3.2 Rationale of study design

This study has been designed as a multi-center, randomized, parallel group, placebo-controlled, double-blind, event-driven trial to provide definitive evidence on the effects of canakinumab on cardiovascular adverse events in patients with recent MI and elevated inflammatory burden as evidenced by elevated hsCRP. This study will also measure the effects of canakinumab on the conversion to NOD as a secondary endpoint. This study design is the most robust clinical trial design to test the hypothesis that anti-inflammatory treatment with canakinumab will reduce major adverse cardiovascular events.

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The design of the extension phase is appropriate to enable the collection of additional long-term safety data for the investigational drug and to provide patients the opportunity to receive treatment with canakinumab until marketed product is available. The study design also allows to evaluate changes in glycemic status following study drug washout in patients with prediabetes in order to assess the durability of any potential antidiabetic effect after study drug discontinuation. Enrollment will be available to all patients who participated in the pivotal phase and who continue to be eligible to receive study drug.

3.3 Rationale of dose/regimen, duration of treatment

Canakinumab 50 mg and 150 mg quarterly

The 50 mg and 150 mg canakinumab dosing schedule has been selected on the basis of anticipated efficacy, safety, and biomarker modeling data. In phase II development, all canakinumab doses up to 300 mg s.c. every other week have been found safe, well tolerated, and free of adverse lipid effects. Canakinumab efficacy in lowering hsCRP, IL-6 and fibrinogen was assessed based on studies CACZ885A2213 and CACZ885I2202. The maximum efficacy of hsCRP lowering in study CACZ885I2202 was at approximately 50 - 75 mg of canakinumab monthly, with persistent lowering across a wide range of higher doses. Therefore, 50 mg monthly as fully efficacious dose and 15 mg monthly as submaximal dose were selected for further development. The optimal dosing interval was examined using data from CACZ885A2213 (diabetes) and from gout studies with canakinumab (data on file). These studies indicated that canakinumab effect on lowering hsCRP was durable for up to approximately 3 months. Further, modeling and simulation methods showed that 150 mg quarterly dosing had similar free IL-1β suppression compared to 50 mg monthly dosing and 50 mg quarterly dosing had similar free IL-1β suppression compared to 15 mg monthly dosing. This conclusion was reached by comparing the doses and regimens based on both the time for maintenance of suppression and the fraction of patients below a specified suppression threshold of 'tissue free' IL-1β. Therefore, canakinumab 50 mg and 150 mg quarterly administration were selected for the doses in this study, CACZ885M2301. The selected doses allow examination canakinumab dose response in preventing recurrent cardiovascular events and to determine if a lower dose than 150 mg would have a favorable risk benefit ratio.

Canakinumab 300 mg quarterly

Given evidence of safety across a wide dosing range, a 300 mg quarterly dosing schedule for canakinumab has also been developed for CACZ885M2301. This allows evaluation of a higher canakinumab dose since the dose needed for adequate IL-1β neutralization within the plaque or systemically in inflammation-based atherosclerosis is not established. Therefore, a higher dose may deliver greater efficacy than the other selected dose, 150 mg quarterly. This 300 mg quarterly dosing regimen also includes an induction period over 2 weeks, dosing at randomization (month 0) and at week 2 (month 0.5), in order to assure that auto-induction of IL-1β pathway is adequately inhibited at study initiation. The complete suppression of IL-1β related gene expression achieved with this early high dose administration, coupled with the continuous canakinumab treatment effect which has been proven to last the entire quarterly dosing period, is expected to minimize the potential for IL-1β rebound. This may be relevant for pathogenesis of atherosclerosis because it is theorized that IL-1 auto-induction provides a

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positive feedback mechanism for vascular disease including atherosclerosis. The lower 50 mg and 150 mg quarterly doses does not include an early high, induction dose regimen to ensure separation of the three canakinumab dose levels included in this protocol and to allow assessment of the impact of the early high dose regimen included in the 300 mg arm on clinical cardiovascular events.

Induction dose in the 300 mg quarterly dose arm

In phase II studies in patients with gout, diabetes, and acute inflammatory conditions, safety of canakinumab across a wide range of doses has not emerged as a major clinical issue. Due to long term suppression of inflammatory biomarkers, quarterly dosing of canakinumab is feasible and likely to be clinically effective. In addition, data in the setting of acute inflammation suggests that higher initial doses of canakinumab that can be achieved through induction are safe and provide an opportunity to ameliorate concern regarding potential auto-induction of IL-1β and to achieve greater early suppression of IL-1β related gene expression. IL-1β auto-induction has been shown in human mononuclear blood, human vascular endothelial, and vascular smooth muscle cells in vitro and in rabbits in vivo where IL-1 has been shown to induce its own gene expression and circulating IL-1β level (Dinarello et al. 1987, Warner et al. 1987a, and Warner et al. 1987b). These studies suggested that IL-1 induced IL-1 gene expression may provide a positive feedback mechanism in the pathogenesis of atherosclerosis and promote atherosclerosis. This consequently suggests that suppression of this feedback mechanism may provide benefits in the atherosclerotic lesion. Specifically, data supporting an induction dose of canakinumab includes the following: In CACZ885A2102, a CAPS mechanism of action study of patients with Muckle Wells Syndrome (N=4), canakinumab treatment with 10 mg/kg i.v. (equivalent to 600 mg i.v.) single dose induced clinical (improved skin lesions and conjuctival injection) and biomarker (hsCRP and SAA) responses in 24 hrs which was durable up to 180 days. In contrast, canakinumab doses of 1 mg/kg i.v. without induction were only durable up to 90 days. Support for more sustained and higher dose canakinumab therapy was also seen in the rheumatoid arthritis proof of concept study CACZ885A2101, where higher doses of canakinumab were required ($\geq$ 3.0 mg/kg i.v.) to achieve a significant clinical response as scored by the ACR system. Furthermore, in the CACZ885A2102 study, analysis of gene expression known to be related to IL-1 β expression, inflammasome activity, and autoinduction of IL-1 β, showed more complete response to higher dose (10 mg/kg i.v.) than lower dose (1 mg/kg i.v.) canakinumab. In addition, IL-1β and inflammasome related gene expression modification began to decrease with the lower dose (1 mg/kg i.v.) compared to the higher dose (10 mg/kg i.v.) between 10 and 12 weeks. Similar results were obtained in the rheumatoid arthritis study CACZ885A2201 where IL-1β related genes were suppressed more with 300 mg s.c. q2weeks dosing than 150 mg q4weeks dosing.

The documented safety record of canakinumab up to doses of 300 mg s.c. every 2 weeks with and without induction dose of 600 mg i.v., study CACZ885A2201 in rheumatoid arthritis patients up to 6 months, 300 mg q1month, study CACZ885H2257 in gout patients up to 6 months, and 150 mg q1month, study CACZ885I2202 in T2DM patients up to 4 months supports the use of this higher dose regimen.

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Thus, the CACZ885M2301 trial regimens will consist of (a) placebo s.c. at randomization (month 0), placebo s.c. at week 2 (month 0.5), placebo s.c. at week 12 (month 3), and then placebo s.c. quarterly; (b) canakinumab 50 mg s.c. at randomization (month 0), placebo s.c. at week 2 (month 0.5), canakinumab 50 mg s.c. at week 12 (month 3), and then canakinumab 50 mg s.c. quarterly; (c) canakinumab 150 mg s.c. at randomization (month 0), placebo s.c. at week 2 (month 0.5), canakinumab 150 mg s.c. at week 12 (month 3), and then canakinumab 150 mg s.c. quarterly; and (d) canakinumab 300 mg s.c. at randomization (month 0), canakinumab 300 mg s.c. at week 2 (month 0.5), canakinumab 300 mg s.c. at week 12 (month 3), and then canakinumab 300 mg s.c. quarterly.

Dosing regimen in extension phase

Every trial participant who continues to be eligible to receive study drug will be offered the option to continue study drug treatment during the extension phase. Consenting patients except those with prediabetes will remain on their pivotal phase assigned treatment arm for the first three extension phase visits (Month 0 to Month 6). After the database from the pivotal phase is locked, participants will be switched to an open-label dose of 150 mg canakinumab at the fourth scheduled extension visit (visit Month 9) (Figure 3-2). The 150 mg dose is predicted to have the highest likelihood of having the most favorable benefit: risk ratio based on biomarker and clinical data from phase II studies in Type 2 diabetics. The final canakinumab dose will be based on the results from the pivotal phase. The transition to an intermediate dose of 150 mg will avoid further placebo treatment until the final dose of canakinumab is implemented at the study sites. The first drug administration as part of the extension will be performed at the first visit of the main drug dispensing period of the extension phase. The first visit of the main drug dispensing period at Month 0 should occur on the same day as the pivotal phase EOS visit. In case the last drug administration of the pivotal phase occurred within 4 weeks before the pivotal phase EOS visit, the study drug administration at the extension phase Month 0 visit will be skipped and the first injection as part of the extension phase will be performed at the Month 3 visit. In contrast to all other participants of the pivotal phase, prediabetic patients will enter a 6-month study drug washout at the beginning of the extension phase after which they will restart study drug administration as part of the extension phase. For participants of the prediabetes washout, the first visit of the subsequent main drug dispensing period of the extension at Month 0 should occur on the same day as the End of Prediabetes Washout visit. At this Month 0 visit study drug washout participants will receive one dose of their assigned pivotal phase blinded treatment arm before they switch to the open-label dose of 150 mg canakinumab at their next visit (visit Month 3) (Figure 3-3).

3.4 Rationale for choice of comparator

This trial is placebo controlled to provide robust evidence on the effects of canakinumab on clinical events and safety as well tolerability. No comparative anti-inflammatory treatment has been shown to date to benefit patients with cardiovascular disease and thus an active comparator arm is not available. All patients in all treatment arms will receive standard of care post-MI background therapy including, but not limited to, lipid lowering, anti-hypertensive, beta blockers, and anti-platelet therapy as appropriate. High dose statin comparator therapy was initially considered as an appropriate active comparator; however, it

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was felt that it would be unethical to restrict use of proven benefit high dose statin therapy to the comparator arm only. No active comparator will be used in the extension phase. Additionally, no placebo drug will be used from extension visit Month 3 onwards (participants of study drug washout period) and from Month 9 onwards (all other participants of extension phase).

3.5 Purpose and timing of interim analyses/design adaptations

Interim analyses (IA) of efficacy, futility and safety will be carried out during the study in order to avoid exposing study patients to ineffective treatment or undue risks or to allow study discontinuation in case of overwhelming efficacy. Two interim analyses of efficacy will be performed when approximately 50% of the target number of patients with primary endpoints have been accumulated and the second one when approximately 75% of the planned number of patients with primary endpoints are available.

Interim analyses for futility will be conducted simultaneously with the analyses of efficacy, and one additional futility analysis may also be performed earlier than the first planned efficacy IA (at approximately 50% primary events), but only after a sufficient number of primary events are accrued, i.e., >25%. The criteria for formal statistical significance at the interim analyses are specified in the data analysis section of the protocol, but details on futility boundaries and stopping rules will be pre-specified in the charter of the Data Monitoring Committee (DMC). The timing and number of safety analyses will also be specified in DMC charter, but these are estimated to occur on a six-month basis (full committee) and on a three-month basis (chair only).

The unblinded results of the interim analyses will be reviewed by the DMC. Investigators, Novartis, and others who are involved in the conduct of the trial, in the analysis of the final trial results, or who have contact with study centers, will remain blinded to the treatment codes and interim analysis results until all monitoring decisions have been made and the database has been locked for final analysis.

4 Population

Participants eligible for this trial will include male and non-child-bearing potential female patients age 18 years and older who (a) have suffered a documented acute myocardial infarction at least 30 days before randomization and (b) have persistent evidence of systemic inflammation on the basis of an hsCRP $\geq$ 2 mg/L despite the use of standard of care post-MI medical therapies. Standard of care post-MI background therapy includes, but is not limited to, lipid lowering, anti-hypertensive, beta blockers, and anti-platelet therapy as appropriate.

In data from the PROVE IT – TIMI 22 trial, 43 percent of a post-MI population screened at 30 days had hsCRP $\geq$2 mg/L despite maximal therapy including high-dose statin (Ridker et al 2005).

In previous registries and studies of post-MI patients, approximately 25 percent are likely to have a diagnosis of T2DM, 35 percent are likely to be pre-diabetic, and 40 percent are likely to be normoglycemic patients. In this trial the following definitions of pre-diabetes and type 2 diabetes at randomizations will be used:

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Definition of randomization Pre-Diabetes

- At visit 1 OR 2 HbA1c of 5.7-6.4% or FPG 100-125 mg/dL (5.6-6.9 mmol/L) (ADA 2010 Clinical Practice Recommendations)

Definition of randomization Type 2 Diabetes

- At Visit 1 (screening) and Visit 2 (Randomization/Baseline) any patient with:
  - Medical history of type 2 diabetes and any patient currently on concomitant anti-diabetic medication

    or
  - HbA1c ≥6.5% (visit 1 and visit 2)

    or
  - FPG ≥ 126 mg/dL (≥7.0 mmol/L) (visit 1 and visit 2).

    or
  - Combination of FPG ≥ 126 mg/dL (≥7.0 mmol/L) and HbA1c ≥6.5% (visit 1 and visit 2)

Definition of Prediabetes at the End of Study Visit

- At randomization and at the EOS visit of the pivotal phase (based on the last available HbA1c and FPG measurement prior to the EOS visit) having prediabetes as defined by HbA1c of 5.7-6.4% or FPG 100-125 mg/dL (5.6-6.9 mmol/L) (ADA 2010 Clinical Practice Recommendations)

The pivotal phase will be an event-driven global trial conducted in the outpatient setting. It is anticipated that approximately 1,400 patients with adjudication committee confirmed cardiovascular endpoints will accrue during the course of the pivotal phase (see Section 9.7 for Power Calculations). To accomplish this goal, it is expected that approximately 17,000 patients will need to be screened in order to randomize approximately 10,000 patients. All participants of the pivotal phase who continue to be eligible to receive study drug will be offered the option to enter the extension phase.

4.1 Inclusion criteria

Patients eligible for inclusion in this study must fulfill all of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Male, or Female of non-child-bearing potential
3. Age ≥ 18 years at Visit 1.
4. Documented spontaneous MI (diagnosed according to the universal MI criteria with or without evidence of ST segment elevation) at least 30 days before randomization. (Thygesen et al 2007)
   - Diagnosis of the qualifying MI should be based on medical history of clinical symptoms consistent with myocardial ischemia associated with elevation of cardiac biomarkers above the 99th percentile of the upper reference limit (preferably troponin)

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OR development of new pathological Q waves regardless of symptoms. For details, refer to the Universal Definition of MI (Thygesen et al 2007).

- Please see below for documentation requirements.
  a. Acute MI (hospitalization records): requires documentation of a rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) or above criteria diagnostic for MIAND evidence of myocardial ischemia as demonstrated by at least one of the following :
     i. Symptoms of ischemia
     i. ECG changes indicative of new ischemia (new ST-T changes or new LBBB)
     ii. Development of pathologic Q waves (please see appendix 3 for definitions of pathological Q waves)
     iii. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
  b. Prior MI (no hospital records for acute event available): requires documentation of any one of the following :
     i. Development of pathological Q waves with or without symptoms (please see appendix 3 for definitions of pathological Q waves)
     ii. Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause
     iii. Pathologic findings of a healed or healing MI
- Patients with MI resulting from PCI or CABG will not be eligible

5. Have an hsCRP ≥ 2 mg/L (collected less than 60 days prior to Visit 2 and performed at the central laboratory, which is a minimum of 28 days after qualifying MI or after any PCI performed separately from qualifying MI) on stable (at least 4 weeks) long term (cardiovascular) medications.

4.2 Exclusion criteria

1. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test
2. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, UNLESS they are
   a. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone or partial or total hysterectomy, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

   [For Croatia only]

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[In Croatia, women who are < 50 years of age must have >2 years of amenorrhea or minimum of 1 year of amenorrhea with FSH levels of ≥40 IU determined on 2 or more occasions at least one month apart]

3. Any of the following concomitant conditions or diseases:
   a. Planned coronary revascularization (PCI or CABG) or any other major surgical procedure.
   b. Major non-cardiac surgical or major endoscopic procedure within the past 6 months prior to Visit 1
   c. Multi-vessel CABG surgery within the past 3 years
   d. Symptomatic patients with Class IV heart failure (HF) (New York Heart Association).
   e. Uncontrolled hypertension (defined as an average SBP >160 mmHg or an average diastolic blood pressure (DBP) >100 mmHg at Visit 1. Patients are allowed to be re-evaluated, at the discretion of investigator for this criterion if anti-hypertensive therapy has been started or increased as a result of initial screening blood pressure above these limits (Mancia et al 2009).
   f. Uncontrolled diabetes as defined by the investigator
   g. Nephrotic syndrome or eGFR < 30 mL/min/1.73 m^2 per MDRD formula or kidney transplant (regardless of renal function), at Visit 1
   h. Known active or recurrent hepatic disorder (including cirrhosis, hepatitis B and hepatitis C (positive or indeterminate central laboratory results), or alanine aminotransferase/ aspartate aminotransferase (ALT/AST) levels > 3 times ULN or total bilirubin > 2 times ULN) atVisit 1
   i. Prior malignancy other than basal cell skin carcinoma
4. A history of alcohol and/or substance abuse that could interfere with the conduct of the trial
5. History or evidence of tuberculosis (TB) (active or latent) infection or one of the risk factors for tuberculosis such as but not limited or exclusive to:
   a. History of any of the following: residence in a congregate setting (e.g. jail or prison, homeless shelter, or chronic care facility), substance abuse (e.g. injection or non-injection) health-care workers with unprotected exposure to patients who are at high risk of TB or patients with TB disease before the identification and correct airborne precautions of the patient
   b. Close contact (i.e. share the same air space in a household or other enclosed environment for a prolonged period (days or weeks, not minutes or hours)) with a person with active pulmonary TB disease within the last 12 months.
   c. Evidence of TB infection (active or latent), at Visit 1, determined by purified protein derivative (PPD) skin test and/or QuantiFERON®-TB Gold (QFT-g) assay as defined by country guidelines (refer to Determination of Tuberculosis Status, p.39).
      i. If presence of TB (active or latent) is established then treatment (according to country guidelines for TB treatment or TB treatment with immunomodulating drugs) must have been initiated or completed prior to randomization per country guidelines.

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ii. In the absence of country TB (active or latent) guidelines, the following has been demonstrated: TB has been treated adequately with antibiotics, cure can be demonstrated, and risk factors resulting in TB exposure and contracting TB have been removed (e.g. the patient does not live anymore in high TB exposure setting).

6. History of ongoing, chronic or recurrent infectious disease
7. Patients with suspected or proven immunocompromised state, including (a) those with evidence of Human Immunodeficiency Virus (HIV) infection; Patients on anti-retroviral therapy are excluded (b) those with any other medical condition which in the opinion of the investigator places the patient at unacceptable risk for participation in immunomodulatory therapy; or (c) those requiring systemic or local treatment with any immune modulating agent in doses with systemic effects e.g. high dose oral or intravenous steroids (> 20 mg prednisone orally daily for > 14 days, > 5 mg prednisone orally daily or equivalent dose of intravenous steroid) or high dose methotrexate (> 15 mg weekly). Topical, inhaled, local steroid use in doses that are not considered to cause systemic effects are permitted.
8. Live vaccinations within 3 months prior to the randomization visit or live vaccinations planned during the trial.
9. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.
10. Patients who have received an investigational drug or device within 30 days (inclusive) of Visit 1, or who are expected to participate in any other investigational drug or device study during the conduct of this trial, except for patients who have an investigational drug eluting stent (DES), provided that they have completed the DES trial. FDA/country-specific drug regulatory authority approved DES devices are permitted.
11. Any biologic drugs targeting the immune system (for example, TNF blockers, anakinra, rituximab, abatacept, tocilizumab)
12. Any life threatening condition with life expectancy < 5 years, other than vascular disease that might prevent the patient from completing the study

Determination of tuberculosis status

Determination of tuberculosis (active or latent) status, either by performing the PPD skin test or the QFT-g assay will be required before administration of study drug and should be performed as defined by country guidelines. Patients need to have given written informed consent before any of these assessments are initiated. Patients who have had a negative PPD skin test or negative QFT-g assay performed within 30 days of screening (Visit 1) will not need repeat testing performed to determine eligibility. All other patients will need tuberculosis (active or latent) status determined at Visit 1.

Any significant findings will be recorded in the “Medical History” section of the eCRF as necessary.

Patients with either a positive PPD or positive or indeterminate QFT-g test may still participate in the study if

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1. Treatment of tuberculosis (active or latent) (according to country guidelines) has been initiated or completed prior to randomization

or

2. Patients with a history of TB who were treated must demonstrate that treatment has been received and further work up (according to country practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis.

or

3. The repeat QFT-g test is negative in patients with an indeterminate QFT-g result at Visit 1.

PPD skin test

A PPD skin test may be initiated to evaluate for an occult infection with TB. The test dose is bioequivalent to 5 tuberculin units (or as according to local standard practice) of standard PPD usually injected intradermally into the volar surface of the forearm. The injection site will be cleansed and the PPD extract will then be injected into the most superficial layer under the skin. If given correctly, the injection should raise a small wheal of about 5 mm, which resolves within 10-15 minutes.

A reaction will be measured in millimeters of indurations (hard swelling) after 48h – 72h. A PPD skin induration > 5 mm is interpreted as positive result. This will determine whether the patients have had a significant reaction to the PPD skin test. In case of a positive PPD skin test, the patient may be further screened for latent TB infection by performing the QFT-g test.

The investigator will either obtain PPD skin tests on his own and be reimbursed by Novartis for its cost or be supplied with them by the Novartis affiliate, depending on the local Novartis policy.

QuantiFERON-TB Gold Assay

A QuantiFERON®-TB Gold (QFT-g) assay may be performed to assess the TB (active or latent) status at baseline on patients as needed.

This blood-based assay is specific for Mycobacterium tuberculosis and is not influenced by previous Bacillus Calmette-Guérin (BCG) vaccination or exposure to other Mycobacteria species. This test, in contrast to the PPD skin test, is also insensitive to a booster effect since the patient is not exposed to the vaccine. The assay measures the production of interferon-gamma and puts it into relation to a negative and a positive control sample.

Details about QFT-g sample processing are described in the central laboratory manual.

Chest x-ray

A chest x-ray may be performed if required by country regulations in case of positive PPD skin test or positive QFT-g assay but will not be part of eligibility assessment.

If in line with country guidelines, a chest x-ray will be sufficient to check eligibility with respect to active TB status prior to randomization. This x-ray should be no more than 30 days old at the time of screening.

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Tuberculosis status will not be re-assessed during the extension phase.

5 Treatment

5.1 Investigational and control treatment

Canakinumab (ACZ885) or matching placebo solution for injection will be provided by Novartis as ready-to-use pre-filled syringes. The sites will receive their first shipment of study treatment only after the first screened patient has been registered in the IVRS/IWRS.

Two strengths and respective corresponding matching placebos will be supplied:

- Canakinumab 50 mg in 0.5 mL solution for injection and one placebo formulation matching to this active drug formulation.
- Canakinumab 150 mg in 1 mL solution for injection and one placebo formulation matching to this active drug formulation.

The study drug will be given as subcutaneous injections at randomization, week 2 (month 0.5), and then quarterly beginning at week 12 (month 3). All injections (double dummy design, two syringes of 1 mL for patients randomized to randomization plan A, one syringe of 1ml and one syringe of 0.5 ml for patients randomized to randomization plan B) will be administered at study sites by trained site staff, facilitating both compliance and long-term follow-up for both safety and efficacy outcomes. Please see Table 5-1 below for planned canakinumab injections at study visits. Study treatment and/or placebo will be given in addition to local standards of care for post-MI patients which may include lipid lowering, anti-hypertensive, beta blockers and anti-platelet therapies and is determined by the responsible treating physician. The sites should make alternative arrangements for those patients likely to miss visits due to travel or other reasons. The minimum time between dosing visits after Visit 3 is 30 days.

Table 5-1 Injection Description

Randomization Plan	Treatment Groups	Injections at all visits excluding Screening, month 0.5 and 1.5 visits	Injections at Visit month 0.5
A	Canakinumab 150 mg sc	1 x canakinumab 150 mg and 1 x matching placebo	2 x placebo matching canakinumab 150 mg
A	Canakinumab 300 mg sc	2 x canakinumab 150 mg	2 x canakinumab 150 mg
A	Placebo	2 x placebo matching canakinumab 150 mg	2 x placebo matching canakinumab 150 mg
B	Canakinumab 50 mg sc	1 x canakinumab 50 mg and 1 x 150 mg matching placebo	1 x placebo matching canakinumab 50 mg 1 x placebo matching canakinumab 150 mg

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B	**Canakinumab 150 mg sc**	**1 x canakinumab 150 mg and 1 x 50 mg matching placebo**	**1 x placebo matching canakinumab 50 mg 1 x placebo matching canakinumab 150 mg**
B	**Placebo**	**1 x 50 mg matching placebo and 1 x 150 mg matching placebo**	**1 x 50 mg matching placebo and 1 x 150 mg matching placebo**

In the extension phase, all participants except for those with prediabetes will remain on their pivotal phase randomization plan and treatment group for the first three extension phase visits (Month 0 to Month 6). After the database from the pivotal phase is locked, participants will be switched to an open-label dose of 150 mg canakinumab at their fourth scheduled extension visit (visit Month 9) (Figure 3-2). The patients will then start to receive one syringe of canakinumab 150 mg in 1 mL solution for injection.

No study drug treatment will be provided for those patients with both randomization and pivotal phase EOS prediabetes during the 6-month study drug washout period. This means that patients participating in the washout will skip two doses of their pivotal phase blinded assigned treatment arm. After the end of the study drug washout, participants will receive one dose of their assigned pivotal phase blinded treatment arm at their first visit of the subsequent main drug dispensing period of the extension (visit Month 0) before they switch to the open-label dose of 150 mg canakinumab at their next visit (visit Month 3) (Figure 3-3).

All participants of the extension phase will remain on the open-label dose of 150 mg canakinumab until the final dose of canakinumab is implemented at the study sites, based on the results from the pivotal phase.

5.2 Treatment arms

Following protocol Amendment 6 patients will be assigned to one of the following 4 treatment arms in a ratio of 1.4 : 1.3 : 1.3 : 2

- Canakinumab 50 mg s.c. at randomization (month 0), placebo s.c. at week 2 (month 0.5) , 50 mg s.c. at week 12 (month 3) and thereafter 50 mg s.c. quarterly
- Canakinumab 150 mg s.c. at randomization (month 0), placebo s.c. at week 2 (month 0.5), 150 mg s.c. at week 12 (month 3) and thereafter 150 mg s.c. quarterly
- Canakinumab 300 mg s.c. at randomization (month 0), week 2 (month 0.5) , week 12 (month 3) and thereafter 300 mg s.c. quarterly
- Placebo s.c. at randomization (month 0), week 2 (month 0.5) , week 12 (month 3) and thereafter placebo s.c. quarterly

with allocation in a 1.3 : 0.7 : 1 ratio to 300 mg, 150 mg and placebo respectively in randomization plan A and 0.6 : 1.4 : 1 to 150 mg, 50 mg and placebo respectively in randomization plan B. All patients will be equally likely to be assigned to randomization plan A or B. Within each of the two randomization plans patients will have a 2:1 probability of being on active treatment. Prior to protocol amendment 6, patients were assigned in a 1:1:1

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ratio to the 300 mg arm, the 150 mg arm or placebo. Across trial parts 1 and 2 this will approximately result in a 1:1:1:1.5 allocation to 300, 150, 50 mg and placebo, respectively. More precisely, given about 743 patients in trial part one and 9257 in trial part 2, the overall patient allocation would be approximately 2253 for both the 300 and 150 mg groups, 2160 for the 50 mg group and 3333 for the placebo group (a 1.01:1.01:0.97:1.5 ratio).

In the extension phase, all participants except for those with prediabetes will remain on their pivotal phase randomization plan and treatment arm for the first three extension phase visits (Month 0 to Month 6). The participants will be switched to a quarterly s.c. injection of an open-label dose of 150 mg canakinumab at their fourth scheduled extension visit (visit Month 9) following database lock of the pivotal phase (Figure 3-2). Prediabetic patients participating in the 6-month study drug washout will remain on their pivotal phase randomization plan and treatment arm only until their first visit of the subsequent main drug dispensing period (visit Month 0) before they switch to the open-label dose of 150 mg canakinumab at their next visit (visit Month 3) (Figure 3-3). All participants of the extension phase will remain on the open-label dose of 150 mg canakinumab until the final dose of canakinumab is implemented at the study sites, based on the results from the pivotal phase.

5.3 Treatment assignment

At pivotal phase Visit 2, all eligible patients will be randomized via Interactive Voice Response System /Web System (IVRS/IWRS) to one of the treatment arms. The investigator or his/her delegate will contact the IVRS/IWRS after confirming that the patient fulfills all the inclusion/exclusion criteria. The IVRS/IWRS will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the patient. The randomization number will not be communicated to the caller.

In trial part 1 prior to the implementation of protocol amendment 6 at each site, there was a single randomization plan. In trial part 2 (following protocol amendment 6) this trial has two randomization plans A and B. The IVRS/IWRS randomly assigns patients to plan (A and B) and treatment. Randomization plan A includes placebo, 150 mg and 300 mg canakinumab arms and therefore, is fully blinded. Patients assigned to randomization plan A will receive two 1 mL injections at each trial visit except at visit 3 (1.5 months). Randomization plan B includes placebo, 50 mg and 150 mg canakinumab arms, and is also fully blinded. Patients assigned to randomization plan B will receive one 1 mL and one 0.5 mL injections at each pivotal phase visit except at visit 3 (1.5 months). The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IVRS/IWRS provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to study drug packs containing each of the study treatment.

In the extension phase all participants except for those with prediabetes will remain on their randomization number assigned at randomization in the pivotal phase until they switch to an

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open-label dose of 150 mg canakinumab at the fourth scheduled extension visit (visit Month 9) (Figure 3-2). Prediabetic patients participating in the 6-month study drug washout will remain on their randomization number only until their first visit of the subsequent main drug dispensing period (visit Month 0) before they switch to the open-label dose of 150 mg canakinumab at their next visit (visit Month 3) (Figure 3-3).

Stratification

Randomization will be stratified by 'time since most recent MI' as follows:

- Post MI ≥ 30 days but < 6 months
- Post MI ≥6 months

Sites will be asked to indicate the patients' glycemic status at the Visit 3 call post randomization as the Visit 1 and Visit 2 lab results are needed for the following categories (see Section 3.1 for definitions):

- Normoglycemia: HbA1c <5.7% at V1 and V2
- Pre-Diabetes: HbA1c 5.7 – 6.4 % or FPG 100-125 mg/dL (5.6-6.9 mmol/L) inclusive at V1 or V2

  Note: To be included in the 6-month study drug washout, a patient must have a prediabetic status at both randomization and the pivotal phase EOS visit, according to the last HbA1c and FPG measurement available at the EOS visit
- T2DM: (patient needs to have one or more of the following)
  - HbA1c ≥ 6.5% OR FPG ≥ 126 mg/dL (≥7.0 mmol/L) at V1 and V2
  - Combination of HbA1c ≥ 6.5% and FPG ≥ 126 mg/dL (≥7.0 mmol/L) as confirmed at V1 and V2
  - Medical history of T2DM and on a current anti-diabetic medication

At the pivotal phase EOS visit sites will be asked to indicate the patients' glycemic status based on the last available lab results and based on the glycemic status at randomization. Patients who are determined to be prediabetic at both randomization and the pivotal phase EOS visit, will be included in the 6-month study drug washout (see Section 4 for definition).

Sites are required to call the IVRS/IWRS at every visit/phone contact to:

- Prescreen: Register the prescreening visit.
- Visit 1: Register the screening visit. The first shipment of study treatment will ONLY be sent once the site registers their first screened patient.
- Visit 2: Register Screen Failures or randomize a patient. For randomization, enter patient's stratification as the time from the index MI to the date of randomization.
- Visit 3: Register the occurrence of the visit and provide glycemic status.
- Obtain medication numbers for randomization (month 0), week 2 (month 0.5), week 12 (month 3), and quarterly dispensing of study treatment thereafter..
- Register a patient who has died or withdrawn consent (pivotal phase).

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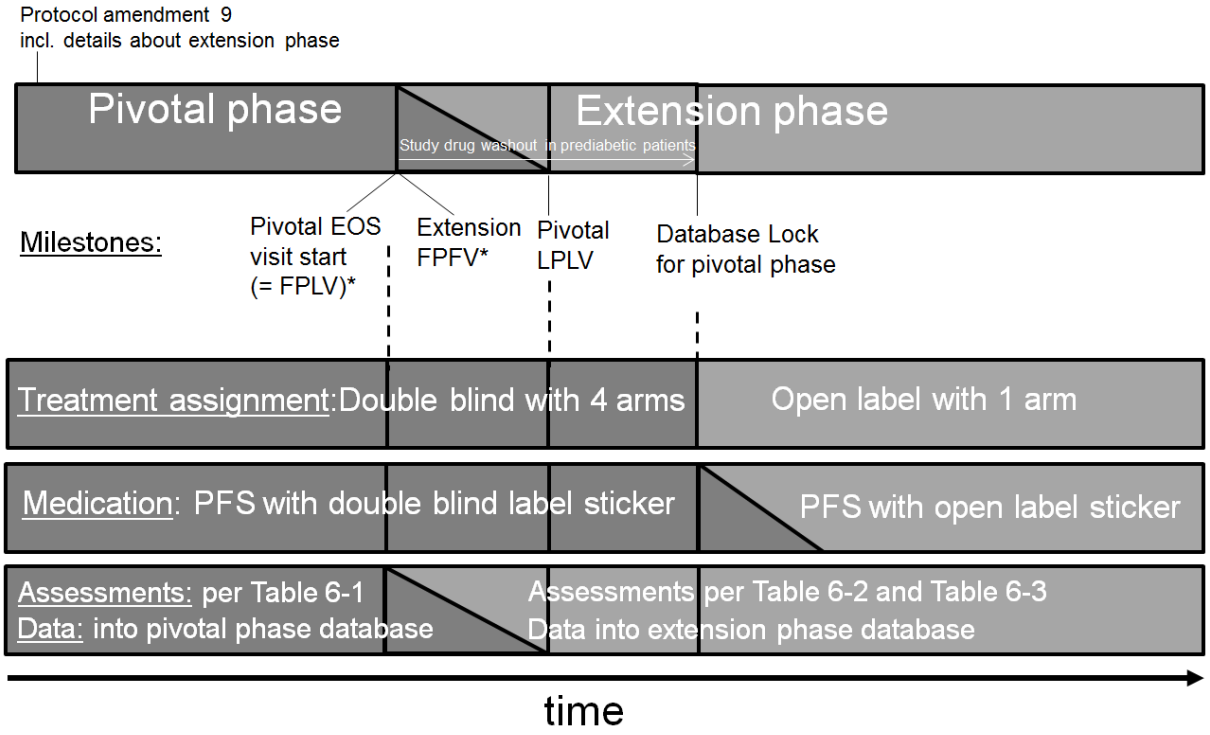
- Register a patient who has completed the pivotal phase (this will only occur when the study has been deemed complete by the DMC or Novartis and the patient returns for the pivotal phase EOS visit); register pivotal phase EOS visit as non-dispensing visit.
- Register a patient who has a glycemic status of "randomization and pivotal phase EOS prediabetes" and transitions into the 6-month study drug washout.
- End of Prediabetes Washout Visit 199: register a patient who has completed the 6-month study drug washout.
- Extension phase Visit 201 (Month 0): Register a patient who consented to participate in the extension phase.

  Register a drug dispensing visit, obtain medication numbers and provide study drug as per pivotal phase treatment arm assignment / randomization number. Note 1: The patients will remain on their assigned pivotal phase treatment arm until Visit 203 (Month 6) (Figure 3-2), except for prediabetic patients participating in the 6-month study drug washout. Such patients will remain on their assigned pivotal phase treatment arm only until Visit 201 (Month 0) (Figure 3-3). Note 2, for patients not participating in study drug washout: In case the last drug administration of the pivotal phase occurred within 4 weeks before the pivotal phase EOS visit, the study drug administration at Visit 201 (Month 0) will be skipped and the first injection as part of the extension phase will be performed at Visit 202 (Month 3).
- Extension phase Visit 202 (Month 3): prediabetic patient who completed the 6-month study drug washout will receive an open-label dose of 150 mg canakinumab and quarterly dispensing of an open-label dose of 150 mg canakinumab thereafter until the final canakinumab dose will be implemented at study sites based on the results from the pivotal phase (Figure 3-3). Patients who did not participate in the study drug washout will remain on their assigned pivotal phase treatment arm (Figure 3-2).
- Extension phase Visit 204 (Month 9): patient will receive an open-label dose of 150 mg canakinumab and quarterly dispensing of an open-label dose of 150 mg canakinumab thereafter until the final canakinumab dose will be implemented at study sites based on the results from the pivotal phase (Figure 3-2).
- Register a patient who has died or withdrawn consent during the extension phase.
- Register a patient who has completed the extension phase (when the patient returns for the extension phase EOS visit).

The randomization scheme for patients will be reviewed and approved by a member of the IIS Biostatistics Quality Assurance Group. The randomization codes will be maintained at Center for Cardiovascular Disease Prevention, Brigham and Woman's Hospital, Harvard Medical School.

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Figure 5-1 Transition from pivotal phase to extension phase



PFS: PreFilled Syringe, FPFV: First Patient First Visit, LPLV: Last Patient Last Visit

*for patients not participating in study drug washout: pivotal phase EOS visit and first extension phase visit are two different study visits that should occur on the same day. (If the last pivotal phase study drug injection before the EOS visit occurred within four weeks of the EOS visit, the first injection from the extension will be skipped). For participants of study drug washout: End of Prediabetes Washout visit and first visit of the main drug dispensing period of the extension phase are two different visits that should occur on the same day.

5.4 Treatment blinding

Patients, investigator staff and external personnel performing the assessments will remain blinded to the identity of the treatment from the time of randomization until the patients switch to the open-label dose of 150 mg canakinumab at extension phase visit Month 3 (only participants of 6-month study drug washout) and visit Month 9 (all patients who did not participate in the study drug washout), respectively. Data analysts will remain blinded to the identity of the treatment from the time of randomization until pivotal phase database lock, using the following methods:

Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the exception of the independent unblinded statistician, programmer and data manager/data coordinator (and assistant as required) who need to have access to prepare safety and efficacy interim analysis reports for the DMC and the bioanalyst and pharmacokineticist (to avoid the unnecessary analysis of placebo samples). These personnel will not be involved in any other trial activities.

The identity of the treatments in trial part 1 and in trial part 2 within each randomization plan (i.e., Plan A and Plan B) will be concealed by the use of double-dummy approach using study

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drugs that are identical in packaging, labeling, schedule of administration and appearance. While investigators will not be blinded as to whether patients in trial part 2 are in randomization plan A or B, the probability of the patient being on active treatment is the same (2:1) in either case. Thus, it is not expected that this introduces any biases.

The study drug injections as part of the extension phase will remain blinded for the data analysts until pivotal phase database lock. The study drug injections received as part of the extension phase will remain blinded to patients, investigator staff and external personnel performing the assessments until patients switch to the open-label dose of 150 mg canakinumab at visit Month 3 (only participants of 6-month study drug washout; see Figure 3-3) and visit Month 9 (all patients not participating in study drug washout; see Figure 3-2), respectively. Until the switch to the open-label dose of 150 mg canakinumab during the extension phase, unblinding will only occur in the case of patient emergencies (see Section 5.5.9), at the time of interim analysis and at the conclusion of the pivotal study phase. In the event a patient becomes unblinded for any reason they may continue study treatment and assessments according to the protocol at the discretion of the investigator.

During the open-label treatment as part of the extension phase, medication with a double blind label will continue to be dispensed until new supplies bearing open-label sticker are available at site. The dispensation of the open-label canakinumab dose during the extension phase with kits bearing a double blind label will be managed by the IVRS/IWRS.

PK, biomarkers, immunological laboratory, hsCRP (from baseline) and canakinumab antibody results will be blinded to the sites and Novartis but will be available unblinded for the DMC analyses to assure patient safety.

5.5 Treating the patient

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

5.5.1 Patient numbering

Each patient is uniquely identified in the study by a **Patient Number**. A center number is also assigned by Novartis to the investigative site. Upon signing the informed consent form, the patient is assigned the next sequential patient number by the investigator. The investigator or his/her staff will contact the IVRS/IWRS and provide the requested identifying information for the patient to register them into the IVRS/IWRS. In the electronic data capture (EDC) system, there will be blank CRF books available labeled with a Patient Number. The site should select the CRF book with a matching Patient Number to enter data.

Once assigned to a patient, the Patient Number will not be reused. If the patient fails to be randomized for any reason, the IVRS/IWRS should be notified within 2 days that the patient was not randomized. The reason for not being randomized will be entered on the Screening Period Phase Disposition eCRF.

The assigned patient numbers will be kept also during the extension phase.

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5.5.2 Dispensing the study treatment

Each study site will be supplied by Novartis with study treatment in packaging of identical appearance per product volume. The first shipment of study treatment will occur once the site has registered their first screened patient in the IVRS/IWRS. All injections should be administered by the site staff only.

The study treatment packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the four formulations provided (2 active and 2 corresponding placebo forms). Investigator staff will identify the two study treatment packages for the patient at each dispensing visit by contacting the IVRS/IWRS and obtaining the medication numbers. Immediately before administering the study treatment, the, investigator staff will detach the outer parts of the labels from the packaging and affix them to the source document (Drug Label Form) for that patient's unique patient number.

For the main drug dispensing period of the extension phase, there will be a transition time. This transition time will be divided into three parts:

- First part from first visit (visit Month 0) until switch to open-label treatment with 150 mg canakinumab (i.e. visit Month 3 for participants of 6-month study drug washout (Figure 3-3), and visit Month 9 for all other patients (Figure 3-2)): Patients will continue to receive their double-blind treatment. The medication dispensing will be managed via IWRS/IVRS.
- Second part from first 150 mg canakinumab open-label treatment (i.e. visit Month 3 for participants of 6-month study drug washout and visit Month 9 for all other patients, respectively) until the final dose is implemented at study sites based on the results from the pivotal phase: Patients will receive 150 mg/1 ml canakinumab in an open-label fashion but with a double-blinded sticker until kits with the 150 mg dose are available at study sites with an open-label sticker. The medication dispensation will be managed via IWRS/IVRS.
- Third part from implementation of the final canakinumab dose at study sites until end of study: Patients will receive the final canakinumab dose with double-blinded sticker until kits with the appropriate dose are available at study sites with an open-label sticker. The medication dispensation will be managed via IWRS/IVRS.

5.5.3 Supply, storage and tracking of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Upon receipt, all study treatment should be stored in the refrigerator at 2-8 degrees C (36-46 degrees F). Study treatment temperature should be verified and documented daily (business days) with a minimal / maximum thermometer or another equivalent temperature recording tool. Clinical supplies are to be dispensed only in accordance with the protocol.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug and no information about the patient.

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The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability ledger. Monitoring of drug accountability will be performed by the field monitor during site visits and at the completion of the trial.

At the conclusion of the study, and as appropriate during the course of the study, the Novartis monitor will arrange the return of all unused, damaged or expired study treatment and a copy of the completed drug accountability ledger to Novartis.

The above will also apply for the extension phase.

5.5.4 Instructions for prescribing and taking study treatment

All randomized patients will receive two subcutaneous injections per visit, beginning at randomization (month 0), week 2 (month 0.5) and then quarterly beginning at week 12 (month 3).

Patients will receive either one injection of canakinumab and one injection of placebo, or two injections of placebo or two injections of canakinumab. Injections will be given after all other study assessments have been completed for the visit. All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF. All drug kits assigned by the IVRS/IWRS will be recorded/databased in the IVRS/IWRS. The investigator should promote compliance by informing the patient that compliance is necessary for the patient's safety and the validity of the study.

Principal investigator or trained staff will select injection site(s) for the study injections, which may be administered subcutaneously in the abdomen and/or extremities.

Instructions for use of the safety syringe can be found in Appendix 4.

During the extension phase, all participants except for those with prediabetes will remain on their pivotal phase assigned treatment arm for the first three visits (Month 0 to Month 6). The participants will be switched to an open-label dose of 150 mg canakinumab at the fourth scheduled extension visit (visit Month 9) (Figure 3-2) until the final dose of canakinumab is implemented at the study sites based on the results from the pivotal phase. During the open-label treatment with a dose of 150 mg canakinumab, only one injection will be administered per visit. Prediabetic participants of the 6-month study drug washout will receive one dose of their assigned pivotal phase blinded treatment arm at their first visit of the subsequent main drug dispensing period of the extension (visit Month 0) before they switch to the open-label dose of 150 mg canakinumab at their next visit (visit Month 3) (Figure 3-3) until the final dose of canakinumab is implemented at the study sites based on the results from the pivotal phase.

5.5.5 Permitted interruptions of study treatment

For patients who are unable to tolerate the protocol-specified dosing scheme, dose interruptions are permitted in order to keep the patient on study treatment. Patients are encouraged to continue study treatment; however, patients are allowed to interrupt and restart medication at any time during the study at the discretion of the investigator.

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These changes must be recorded on the Dosage Administration Record CRF (eCRF).This will also apply for the extension phase.

5.5.6 Concomitant treatment

The investigator should instruct the patient to notify the study site about any new medications he/she takes after signing the informed consent. All medications and significant non-drug therapies (including physical therapy and blood transfusions) taken within 30 days of screening and administered after the patient has signed informed consent must be listed on the appropriate Concomitant Medications and or Procedures and Significant Non-Drug Therapies eCRF. Prior treatment for TB infection should be listed on the Concomitant Medications eCRF. Influenza vaccines administered two years prior to study start and pneumococcal vaccines administered five years prior to study start should be recorded on the Prior Influenza Vaccine eCRF and Prior Pneumococcal Vaccine eCRF, respectively. Vaccinations taken during the trial should be reported on the Concomitant Vaccination eCRF.

Patients who are on warfarin or warfarin like treatment with narrow therapeutic index should have their international normalized ratio (INR) measured locally and warfarin or warfarin like treatment dose adjusted accordingly within one month from starting study treatment. This is a general precautionary measure because canakinumab is not expected to interact with warfarin.

Also for the extension phase the investigator should instruct the patient to notify the study site about any new medications he/she takes after signing informed consent.

5.5.7 Prohibited treatment

Use of any treatments below is NOT allowed after the start of study treatment due to potential increase in immunosuppressant related concomitant conditions. They are prohibited for the duration of the study and for at least 90 days after discontinuation of study treatment. This will also apply to the extension phase.

If a patient chooses to continue one of the medications below, they would still be required to be followed as per protocol to assess for any potential study endpoints during the pivotal phase. During the extension phase, patients would still be required to be followed as per protocol to assess for any adverse events. If a patient stops taking any of the below prohibited medications they are eligible to restart study treatment 90 days after stopping the prohibited medication, at the discretion of the investigator.

- Any anti retro-virals and / or any biologic drugs targeting the immune system (e.g., TNFα blockers, anakinra, rituximab, abatacept, tocilizumab)
- immune suppressive drugs: e.g. high dose systemic oral or intravenous steroids (> 20 mg prednisone orally daily for >14 days, > 5 mg orally prednisone daily, or equivalent dose of intravenous steroid) or high dose methotrexate (> 15 mg weekly). (Topical, inhaled, local steroid use in doses that are not considered to cause systemic effects are permitted.)
- Live vaccines within 90 days of study treatment.

  If a patient receives a live vaccine during this trial the next scheduled study treatment will be administered no earlier than 90 days from the administration of the live vaccine.

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5.5.8 Interruption and Discontinuation of study treatment and premature patient withdrawal

The investigator should interrupt or discontinue study treatment for a given patient if, on balance, he/she believes that continuation of study treatment would be detrimental to the patient's well-being. If any patient interrupts or discontinues study treatment, the site is required to follow the patient, as per the study assessment schedule (either by phone or on site visits) until the site has been notified by Novartis that the study has been deemed complete. This will also apply to the extension phase.

Study treatment *must* be discontinued under the following circumstances;

- Withdrawal of informed consent. Study treatment may only be resumed if the patient has re-consented to participation and if the Investigator deems it appropriate to re-initiate study treatment. After the patient re-signs the ICF but prior to restarting study treatment, the Investigator must perform a thorough review of new medical histories and concomitant medication changes from the time corresponding to when the patient left the trial until he/she rejoined. New medical histories must be added to the Adverse Event eCRF and medication changes to the Concomitant Medication eCRF. Additionally, serum chemistry and hematology laboratory evaluations must be reviewed prior to resuming study treatment (Note: if serum chemistry and hematology results were obtained within 6 months prior to resuming study treatment, they do not need to be repeated at the central laboratory; if they are not available within 6 months a blood sample must be drawn and results reviewed by the Investigator prior to dosing the patient).
- Pregnancy. Patients must discontinue study treatment if pregnant; however, study treatment can be resumed in the future after consultation with the Sponsor providing the patient has stopped breast-feeding, has an appropriate clinical profile (i.e. safety laboratories, medical history, adverse events, concomitant medications) and there is documented evidence in the patient chart that the patient is of post-menopausal status per Section 4.2 Exclusion 2.
- Use of prohibited treatment as per Section 5.5.7
- Presence of any malignancy, other than excised basal cell skin carcinoma
- Any other protocol deviation that results in a significant risk to the patient's safety

Any of the following laboratory abnormalities

Clinical Symptoms as noted below, without regard to Liver Function Test's (LFT)

- A jaundice like event
- Any serious adverse event (SAE) indicative of fatal or non-fatal hepatitis, liver failure or its complications

LFT elevations and Clinical Symptoms

- ALT or AST > 3X ULN
- Clinical symptoms suggestive of hepatic dysfunction – such as general malaise, fatigue, abdominal pain, nausea, vomiting or rash with eosinophilia

Asymptomatic elevations of ALT / AST /T. Bilirubin

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- ALT or AST > 3x ULN with a T. Bilirubin > = 2x ULN but with no notable increase in ALP to > 2 X ULN

Asymptomatic isolation of elevations of ALT or AST

- ALT or AST > 8 x ULN discontinue study treatment if elevation persists > 48 hrs
- ALT or AST ≥ 5x ULN ≤8x ULN discontinue study treatment if elevation persists > 2wks.
- ALT or AST≥ 3x ULN <5 ULN discontinue medication at the discretion of the investigator

Asymptomatic isolation elevation of T. Bilirubin

- T. Bilirubin ≥ 3x ULN discontinue if elevation persists > 48 hours

Study treatment may be restarted at the discretion of the investigator, if the reason for withdrawal of study treatment has resolved. Every effort should be made to restart study treatment, if deemed appropriate by the investigator(s). If subjects are rechallenged due liver function laboratory evaluations, they should be followed closely. The subject should be made aware of the potential risk, and consent to the rechallenge, and the Institutional Review Board (IRB) consulted.

The appropriate personnel from the site and Novartis will assess whether study treatment should be discontinued for any patient whose treatment code has been broken inadvertently for any reason. This will also apply for the extension phase until patients switch to open-label administration of canakinumab starting at visit Month 3 (participants of 6-month study drug washout) and visit Month 9 (all patients not participating in study drug washout), respectively.

Patient Status

Patients may voluntarily withdraw from the study for any reason at any time; however, they must be reminded that the site will attempt to obtain a vital status yearly and at the conclusion of the pivotal phase to assess for any potential study endpoints. The site will also attempt to obtain a vital status yearly during the extension phase. The patient contact information should be reviewed with the patient at every scheduled study visit to ensure it is up to date. If local regulations permit, the patient should be asked to provide the contact information for a friend or relative as well as their primary care physician (PCP).

Study Treatment Discontinuation: If premature discontinuation of study treatment occurs for any reason, the investigator must make every effort to determine the primary reason for a patient's premature discontinuation from treatment. Patients who discontinue study treatment should NOT be considered withdrawn from the study. For any patient who chooses to discontinue study treatment, the site must capture this information on the Drug Accountability Record eCRF and the patient should not be registered as discontinued in IVRS/IWRS unless they have withdrawn consent from all study follow-up. The patient should be encouraged to return for scheduled visits after discontinuation of study medication. If the patient refuses onsite visits, the patient, at minimum, should be encouraged to be followed by telephone per the assessment schedule, as every effort must be made by sites staff to follow patients for cardiovascular events and health status. For telephone visits, as much information should be collected as possible (vital status, study endpoints, adverse events, etc). If, at the end of study,

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contact is made to the patient (or on site visit) to assess a health status; the patient will be deemed “completed”.

Lost to-Follow-up: Sites must make every effort to reach patients who fail to return for visits, or become lost to follow-up for any reason, as all patients must be accounted for, at the EOS, to assess for study endpoints. The investigator must show "due diligence" by documenting in the source documents the steps taken to contact patients who are lost to follow-up (i.e. those patients whose life or death status is unclear because they fail to appear for study visits without stating an intention to withdraw). Steps taken include dates of telephone calls, registered letter confirmations, and etc. Sites will be requested to complete the Visit Information eCRF at the regularly scheduled study time points to document the attempts made to contact a person. “Lost to Follow Up” information will be captured on the Study Phase Completion eCRF only if sites are unable to obtain a status on a patient at the end of the study. It is permissible for a patient to contact the site to return for a scheduled clinic visit, at which time their status should then be updated in the systems appropriately. Patient will maintain the previously provided Patient Number and resume study activities based upon their original randomization date.

Withdraw Consent: Any patient who withdraws their consent to participation of study procedures, including telephone contacts to assess health status, will have this information captured on the Study Phase Completion eCRF, which will prompt annual completion of the Survival Information eCRF. To complete the Survival Information page, sites will be asked to check public registries on an annual basis to try and obtain a health status on their patients. Patients may re-consent at any time to resume their participation in the trial. Patients will maintain the previously provided Patient Number and resume study activities based upon their original randomization date. Patients who discontinue study treatment prematurely will not be replaced by an equal number of newly enrolled patients.

The following will apply to the extension phase:

Patients may voluntarily withdraw from the study for any reason at any time. The patient contact information should be reviewed with the patient at every scheduled study visit to ensure it is up to date. If local regulations permit, the patient should be asked to provide the contact information for a friend or relative as well as their primary care physician (PCP).

Study Treatment Discontinuation: If premature discontinuation of study treatment occurs for any reason, the investigator must make every effort to determine the primary reason for a patient’s premature discontinuation from treatment. Patients who discontinue study treatment should NOT be considered withdrawn from the study. For any patient who chooses to discontinue study treatment, the site must capture this information on the Drug Accountability Record eCRF and the patient should not be registered as discontinued in IVRS/IWRS unless they have withdrawn consent from all study follow-up. The patient should be encouraged to return for scheduled visits after discontinuation of study medication. If the patient refuses onsite visits, the patient, at minimum, should be encouraged to be followed by telephone per the assessment schedule, as every effort must be made by sites staff to follow patients for health status.

Lost to-Follow-up: Sites must make every effort to reach patients who fail to return for visits, or become lost to follow-up for any reason, as all patients must be accounted for. The

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investigator must show "due diligence" by documenting in the source documents the steps taken to contact patients who are lost to follow-up (i.e. those patients whose life or death status is unclear because they fail to appear for study visits without stating an intention to withdraw). Steps taken include dates of telephone calls, registered letter confirmations, and etc. Sites will be requested to complete the Visit Information eCRF at the regularly scheduled study time points to document the attempts made to contact a person. “Lost to Follow Up” information will be captured on the Study Phase Completion eCRF only if sites are unable to obtain a status on a patient at the end of the study. It is permissible for a patient to contact the site to return for a scheduled clinic visit, at which time their status should then be updated in the systems appropriately. Patient will maintain the previously provided Patient Number and resume study activities based upon their original randomization date.

Withdraw Consent: Any patient who withdraws their consent to participation of study procedures, including telephone contacts to assess health status, will have this information captured on the Study Phase Completion eCRF, which will prompt annual completion of the Survival Information eCRF. To complete the Survival Information page, sites will be asked to check public registries on an annual basis to try and obtain a health status on their patients.

5.5.9 Emergency unblinding of treatment assignment

Emergency unblinding should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency code breaks are performed using the IVRS/IWRS. When the investigator contacts the system to unblind a patient, he/she must provide the requested patient identifying information and confirm the necessity to unblind the patient. The investigator will then receive details of the drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the Clinical Trial Head that the code has been broken.

It is the investigator’s responsibility to ensure that there is a dependable procedure in place to allow access to the IVRS/IWRS at any time in case of emergency. The investigator will provide:

- protocol number
- study drug name
- patient number

In addition, oral and written information to the subject must be provided on how to contact his/her backup in case of emergency, or when he/she is unavailable, to ensure that unblinding can be performed at any time.

Any patient who is unblinded will continue in the study and may continue receiving study medication as per protocol. This also applies for the extension phase while patients are still on their assigned blinded treatment arm.

5.5.10 Study completion and post-study treatment

The study closeout will be initiated once the study has reached its primary endpoint of 1,400 patients with primary CV events. At this time point sites will be notified to bring back all

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study patients for a pivotal phase EOS visit. At this time patients who have pivotal phase EOS status obtained will be deemed completed for the pivotal phase. At this time, any patient who has signed the informed consent, but has not been randomized into the trial will not be eligible to proceed to randomization and should be registered as a screen failure.

Once the pivotal phase is deemed successfully completed (1,400 primary CV events reached) or is stopped by the DMC recommendation of overwhelming efficacy (prior to 1,400 primary CV events reached) or by Novartis the following will take place

- All patients with a glycemic status of prediabetes from both randomization and pivotal phase EOS visit will proceed into the 6-month study drug washout
- All other patients who continue to be eligible to receive study drug and consent to participate in the extension phase will continue study drug treatment. The extension phase will continue in an individual country for a minimum of two years from the date of the first patients enrolled in that country. The maximum duration of the extension phase will be 2.5 years from the date of the first patient enrolled in that country or until marketed product is available in that country, whichever comes first. The extension phase is then deemed complete while safety follow-up is anticipated to be continued in registries following study results and discussion with Health Authorities.
- All patients with a glycemic status of prediabetes who completed the 6-month study drug washout and consent to participate in the main drug dispensing period of the extension phase will continue with the extension as noted above and restart study drug treatment.

5.5.11 Early study termination

Novartis is committed to follow the IHC Harmonized Tripartite Guidelines for Good Clinical Practice (GCP) in implementation of this trial. The sponsor can terminate the study prior to completion of the trial in the case of a probable negative risk-benefit balance. Furthermore, the study can be terminated at any time for any reason by Novartis. Should this be necessary, patients should be seen as soon as possible and treated as described in Section 6. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 lists all of the assessments of the pivotal phase and indicates with an "x" when the visits are performed. Patients should be seen for all visits on the designated day or as close to it as possible. The study assessment schedule below outlines all procedures performed on patients at scheduled visits. The administration of study treatment is performed as per the visit assessment schedule at study sites by trained site staff after the completion of all other assessments.

The visit assessments listed below are for the estimated timeframe a patient would participate in the study. This is an event driven trial and will be stopped when the target number of primary cardiovascular endpoints have been accrued (please see Section 9 for details). All patients will continue study treatments and visits until the event target has been reached. Patients who complete the 36 months will still be required to return to the clinic every 6

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months for study assessments and quarterly for study treatment until notified by the site staff of pivotal phase completion. Only when the site staff has been notified of the pivotal phase completion by Novartis will the patients with a glycemic status of prediabetes from both randomization and pivotal phase EOS visit be asked to enter the 6-month study drug washout at their pivotal phase EOS visit.

Patients should attend visits, where labs are drawn, in a fasting state of 10 hours.

Pre-screening is a key element to successfully identifying the correct patients to be screened for this clinical study. All patients should have an available hsCRP value prior to the time of screening (Visit 1). The available hsCRP value should be at least 28 days after a cardiovascular event or procedure or major surgical procedure, and must be less than 60 calendar days prior to screening (Note: centrally-performed hsCRP results must be obtained less than 60 calendar days prior to Visit 2 to be used to evaluate Inclusion criterion 5, Section 4.1). The Pre-screening visit should be used after review of the patient's charts to determine patient's eligibility and to obtain an hsCRP value. Patients with a prescreen hsCRP $\geq$ 2 mg/L from the central laboratory do not require a second hsCRP at Visit 1, providing the prescreen hsCRP blood sample is drawn less than 60 days prior Visit 2 and the patient is on a stable (at least 4 weeks) long term (cardiovascular) medications.

Converting to T2DM: Any patient who is reported as having an elevated HbA_{1c} and/or FPG as defined in Section 4, will need to have an unscheduled visit within 6 weeks following the first elevated HbA_{1c} and/or FPG result to assess for conversion from pre-diabetes to T2DM.

Deterioration in Glycemic Control in T2DM Patients: Patients with a HbA_{1c} <7% at randomization (Visit 2) and an elevated $HbA_{1c} \geq 7.5\%$ at Visit 5/Month 6 or beyond, will need to have an unscheduled visit within 6 weeks following the first result to confirm the HbA1c $\geq$ 7.5%. Please refer to Section 6.6.1 for more information.

Discontinuation of study treatment: It is highly encouraged that patients who discontinue study treatment still attend regularly scheduled clinic visits. If the patient does not attend the scheduled visit, site staff are required to make a telephone contact with the patient according to the visit schedule (i.e., every 3 months) to assess for any potential study endpoints and record as appropriately in the eCRFs.

For patients whose treatment is stopped as a result of a data monitoring committee recommendation to suspend treatment in one dose group, follow-up for cardiovascular (CV) and safety events will continue. Since these patients will not receive further study medication, less frequent follow-up will be conducted every 6 months.

Withdrawal of consent or Lost to Follow-Up: Sites are required to provide an annual update in the eCRF's for any patient who has a status of Withdrawal of consent. Please see Section 5.5.8 for any patient who fails to appear for on site visits the study staff will be required to complete the Visit Information eCRF.

For any patients who suffer from a stroke during the pivotal phase please see Section 6.6.5 for details

Sites are required to call the IVRS/IWRS at the prescreening and screening visit and at each visit to register their patient's status and if applicable, receive the medication numbers to

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dispense treatment. Dispensing of medication should be the last assessment performed at each visit.

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Table 6-1 Assessment schedule of pivotal phase

Visit	Pre-Screen	1	2	2.5	3	4	5	6	7	8	9	10	11	12,16, 20,24[8]	13,17, 21, 25[8]	14,18, 22,26[8]	15,19, 23,27[8]	End of Study (EOS)
Month		-1	**0**	**0.5**	**1.5**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27,39, 51,63…**	**30,42, 54, 66…**	**33,45, 57,69…**	**36,48, 60,72…**	**event driven**
Obtain informed consent		X																
Prescreening Informed Consent	X																	
Height		X																
Inclusion/Exclusion		X																
Labs for entry criteria only:, HIV Screen, HBsAg and HCV antibody [For Japan only] [In Japan, HBc antibody and HBs antibody are additionally included]		X																
Hs-CRP	X[10]	X[7]	X	X	X	X	X	X	X		X		X		X		X	X
Determination of tuberculosis status[1]		X																
Demography																		
Demography		X																
History of CV Disease		X																
Medical History/Current Conditions		X																
Family History of CV disease			X															
Smoking & Alcohol History			X															
Treatment Assessments																		
Call IVRS/IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug Administration			X	X		X	X	X	X	X	X	X	X	X	X	X	X	
Prior & Concomitant Antidiabetic & CVD Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications[11]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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Visit	Pre-Screen	1	2	2.5	3	4	5	6	7	8	9	10	11	12,16, 20,24[8]	13,17, 21, 25[8]	14,18, 22,26[8]	15,19, 23,27[8]	End of Study (EOS)
Month		-1	**0**	**0.5**	**1.5**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27,39, 51,63…**	**30,42, 54, 66…**	**33,45, 57,69…**	**36,48, 60,72…**	**event driven**
Efficacy Assessments																		
Potential endpoint assessment				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HbA1c & FPG (all patients)[2]		X	X	X	X	X	X	X	X		X		X		X		X	X
Safety Assessments																		
Physical Exam			X						X				X				X	X
Vitals (includes BMI, weight, waist circumference)		X	X	X	X	X	X	X	X		X		X		X		X	X
ECG			X						X				X				X	X
Standard Hematology & Chemistry		X	X	X	X	X	X	X	X		X		X		X		X	X
Fasting Lipid Profile[3]		X	X	X	X	X	X	X	X		X		X		X		X	X
Other Biomarkers[4]			X			X			X				X				X	X[12]
Immunological (e.g. ANA) Screen			X															X[12]
Immunogenicity (IG) (Anti-canakinumab Ab)			X						X				X					X[12]
canakinumab (PK)			X						X				X					X[12]
IL-1β (PD)			X						X				X					X[12]
Urinalysis including albumin/creatinine ratio (in patients with T2DM or pre-diabetes at baseline)			X			X			X						X			X
AE (prompting for infections)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test in women[9]			X															X

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Visit	Pre-Screen	1	2	2.5	3	4	5	6	7	8	9	10	11	12,16, 20,24[8]	13,17, 21, 25[8]	14,18, 22,26[8]	15,19, 23,27[8]	End of Study (EOS)
Month		-1	**0**	**0.5**	**1.5**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27,39, 51,63…**	**30,42, 54, 66…**	**33,45, 57,69…**	**36,48, 60,72…**	**event driven**
Other																		
Pharmacogenetics[6]			X															
Pharmacogenomic[6]			X			X			X									
EQ-5D[5]			X			X	X		X								X	X
SF-36[5]			X		X	X	X	X	X									
MFSI-SF[5]			X		X	X	X	X	X									
Prompt for macular degeneration		X					X		X		X		X		X		X	X
Patient Education and Counseling			X															

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Visit	Pre-Screen	1	2	2.5	3	4	5	6	7	8	9	10	11	12,16, 20,24[8]	13,17, 21, 25[8]	14,18, 22,26[8]	15,19, 23,27[8]	End of Study (EOS)
Month		-1	0	0.5	1.5	3	6	9	12	15	18	21	24	27,39, 51,63…	30,42, 54, 66…	33,45, 57,69…	36,48, 60,72…	event driven

[1] Please see protocol Section 4.2 Determination of tuberculosis status for details.

[2] Diagnosis of diabetes or failure of glycemic control based on HbA1c data (and/or FPG for diagnosis of diabetes) should be verified by a repeat HbA1c and FPG within 6 weeks of the initial observation.

[3] Patient must have fasted 10 hours for this test. Triglycerides (TG), total cholesterol, HDL cholesterol, LDL cholesterol, VLDL cholesterol and non-HDL cholesterol. LDL Cholesterol, VLDL cholesterol and non-HDL cholesterol will be calculated unless triglycerides > 400 mg/dL in which case a direct LDL cholesterol assay will be employed.

[4] A panel of biomarkers may include but are not limited to: IL-1Ra, IL-6, IL-18,leptin, adiponectin (total and high MW), TNFα, PAI-1 and fibrinogen. Biomarker measurements are at randomization, Month 3, Month 12 and EOS in a subset of patients in predefined countries described in the laboratory manual. Additionally, in a subset of patients participating in the biomarker substudy as outlined in the laboratory manual, an additional blood collection for biomarkers will occur on an annual basis.

[5] Please see Section 6.6.4 and Section 6.6.5 for administration of the questionnaires in addition to the use of the modified Rankin questionnaire.

[6] Pharmacogenetics and Pharmacogenomics will be collected in a subset of patients in defined countries. Optional for patients and will not exclude them from study participation if declined but encouraged.

[7] Patients with a prescreen hsCRP ≥ 2 mg/L from the central laboratory do not require an hsCRP at Visit 1, providing the centrally-performed prescreen hsCRP is less than 60 days prior Visit 2 and the patient is on stable (at least 4 weeks) long term (cardiovascular) medication.

[8] This sequence of visits will repeat until the study is deemed complete and sites are notified by the Sponsor to have all patient return for the EOS assessments

[9] Mandatory for all women, regardless of menopause or surgical history.

[10] The pre-screening hs-CRP value should be noted in the patient chart.

[11] Includes prior treatment for tuberculosis as well as prior flu and pneumococcal vaccinations and all concomitant vaccinations (Section 5.5.6)

[12] Upon approval by Novartis, the Investigator (in select countries) may collect EOS frozen blood samples prior (ideally within 3 months) to the scheduled EOS visit.

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Table 6-2 lists all of the assessments of the extension phase for patients not participating in the 6-month study drug washout. The table indicates with an "X" when the visits are performed. Patients should be seen for all visits on the designated day or as close to it as possible. The study assessment schedule below outlines all procedures performed on patients at scheduled visits. The administration of study treatment is performed as per the visit assessment schedule at study sites by trained site staff after the completion of all other assessments. The first drug administration as part of the extension phase will be performed at the first visit of the extension phase. The first visit of extension phase at Month 0 (visit 201) should occur on the same day as the pivotal phase EOS visit (Figure 3-2). In case the last drug administration of the pivotal phase occurred within 4 weeks before the pivotal phase EOS visit, the study drug administration at the extension phase Month 0 visit will be skipped and the first injection as part of the extension phase will be performed at the Month 3 visit (visit 202). If the pivotal phase EOS visit and the first visit of the extension phase cannot occur on the same day, the Investigator must perform a thorough review of new medical histories and concomitant medication changes from the time of the last trial visit until the first visit of the extension phase. New medical histories must be added to the Adverse Event eCRF and medication changes to the Concomitant Medication eCRF. After signing the ICF, the patient should enter the extension phase at the visit number corresponding to the visit that would be scheduled if the pivotal phase EOS visit and first visit of the extension phase occurred on the same day. However, if this visit number is greater than Month 9 (Visit 204), the patient should enter the extension phase at visit Month 9 (Visit 204). The first visit of the extension phase should occur within 18 months of the last visit of the pivotal phase. The visit assessments listed below are for the estimated timeframe a patient would participate in the study. The extension phase will continue in an individual country for a minimum of two years from the date of the first patients enrolled in that country. The maximum duration of the extension phase will be 2.5 years from the date of the first patient enrolled in that country or until marketed product is available in that country, whichever comes first.

Discontinuation of study treatment: It is highly encouraged that patients who discontinue study treatment still attend regularly scheduled clinic visits. If the patient does not attend the scheduled visit, site staff are required to make a telephone contact with the patient according to the visit schedule (i.e. every 3 months) to assess for any adverse event and record as appropriately in the eCRFs.

Sites are required to call the IVRS/IWRS at each visit to register their patient's status and if applicable, receive the medication numbers to dispense treatment. Dispensing of medication should be the last assessment performed at each visit.

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Table 6-2 Assessment schedule of extension epoch for patients not participating in study drug washout

Visit Number	201[2]	202	203	204[5]	205	206	207	208	209	210	299 (End of extension[1])
Month	0[2]	3	6	9	12	15	18	21	24	27	30[1]
Obtain informed consent	X										
Pregnancy test in women[3]	X[7]										X
Call IVRS/IWRS	X	X	X	X	X	X	X	X	X	X	X
Prior & Concomitant Antidiabetic & CVD Medications	X[6,7]	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X[6,7]	X	X	X	X	X	X	X	X	X	X
AE (prompting for infections, malignancies, CV events)[8]	X[6,7]	X	X	X	X	X	X	X	X	X	X
Drug administration	X[2]	X	X	X[5]	X	X	X	X	X	X	
Study phase completion form											X
EQ-5D[4]					X				X		X
Vitals (includes BMI, weight, waist circumference)					X				X		X

[1] The extension phase will continue in an individual country for a minimum of two years from the date of the first patients enrolled in that country. The maximum duration of the extension phase will be 2.5 years from the date of the first patient enrolled in that country or until marketed product is available in that country, whichever comes first.

[2] First visit of extension phase at Month 0 (Visit 201) should occur on the same day as the pivotal phase EOS visit. In case the last drug administration of the pivotal phase occurred within 4 weeks before the pivotal phase EOS visit, the study drug administration at the extension phase visit 201 (Month 0) will be skipped and the first injection as part of the extension phase will be performed at visit 202 (Month 3). Prior & Concomitant Antidiabetic & CVD Medications, Concomitant Medications, Vitals and AE assessment are not required at first visit of extension phase (Month 0, Visit 201) if they are performed as part of the pivotal phase EOS visit.

[3] Mandatory for all women, regardless of menopause or surgical history. Pregnancy test to be performed locally.

[4] Please see Section 6.6.4 for administration of the questionnaire.

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[5] Visit 204 (Month 9) will be the first scheduled visit at which an open-label dose of 150 mg canakinumab will be administered. The intermediate dose of 150 mg canakinumab will be administered until the final dose of canakinumab is implemented at the study sites based on the results from the pivotal phase.

[6] Adverse Events and Concomitant Medications ongoing from the pivotal phase EOS visit must be re-entered into the extension phase visit Month 0 (Visit 201) Adverse Event eCRF and Concomitant Medication eCRF, respectively.

[7] Adverse Events, Concomitant Medications and a urine pregnancy test will be newly assessed for patients who do not have the pivotal phase EOS visit on same day as the first visit of the extension phase.

[8] New medical histories must be added to the Adverse Event eCRF.

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Table 6-3 lists all of the assessments of the extension phase for patients with prediabetic status at both randomization and pivotal phase EOS visit who participate in the 6-month study drug washout with no study drug administration. The table indicates with an "X" when the visits are performed. Patients should be seen for all visits on the designated day or as close to it as possible. The study assessment schedule below outlines all procedures performed on patients at scheduled visits. The administration of study treatment is performed as per the visit assessment schedule at study sites by trained site staff after the completion of all other assessments. During the study drug washout, prediabetic patients will skip two doses of their pivotal phase blinded assigned treatment arm. The pivotal phase EOS glycemic status will be assessed based on the last HbA1c and FPG data available at the EOS visit. If no HbA1c value is available from the End of Prediabetes Washout visit or if a diabetes diagnosis is only based on one FPG value of ≥ 126 mg/dL (≥ 7 mmol/L) from the End of Prediabetes Washout visit, an unscheduled visit should be conducted within 6 weeks. At their first visit of the subsequent main drug dispensing period of the extension phase (visit Month 0) study drug washout participants receive one dose of their assigned pivotal phase blinded treatment arm before they switch to the open-label dose of 150 mg canakinumab at their next visit (visit Month 3). The first visit of the main drug dispensing period of the extension phase (Month 0, Visit 201) should occur on the same day as the End of Prediabetes Washout visit (Visit 199) (Figure 3-3). If the End of Prediabetes Washout visit and the first visit of the main drug dispensing period of the extension phase cannot occur on the same day, the Investigator must perform a thorough review of new medical histories and concomitant medication changes from the time of the last attended trial visit until the first attended visit of the main drug dispending period of the extension phase. New medical histories must be added to the Adverse Event eCRF and medication changes to the Concomitant Medication eCRF. After signing the ICF, the patient should enter the main drug dispensing period of the extension phase at the visit number corresponding to the visit that would be scheduled if the End of Prediabetes Washout visit and first visit of the main drug dispensing period of the extension phase occurred on the same day. However, if this visit number is greater than Month 3 (Visit 202), the patient should enter the extension phase at visit Month 3 (Visit 202). The first visit of the main drug dispensing period of the extension phase should occur within 18 months of the last visit of the pivotal phase. The visit assessments listed below are for the estimated timeframe a patient would participate in the study. The extension phase will continue in an individual country for a minimum of two years from the date of the first patients enrolled in that country. The maximum duration of the extension phase will be 2.5 years from the date of the first patient enrolled in that country or until marketed product is available in that country, whichever comes first.

Discontinuation of study treatment: It is highly encouraged that patients who discontinue study treatment still attend regularly scheduled clinic visits. If the patient does not attend the scheduled visit, site staff are required to make a telephone contact with the patient according to the visit schedule (i.e. every 3 months) to assess for any adverse event and record as appropriately in the eCRFs.

Sites are required to call the IVRS/IWRS at each visit to register their patient's status and if applicable, receive the medication numbers to dispense treatment. Dispensing of medication should be the last assessment performed at each visit.

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Table 6-3 Assessment schedule of extension epoch for prediabetic patients participating in 6-month study drug washout

Visit Number	199[1] (End of Prediabetes Washout)	201[3]	202[8]	203	204	205	206	207	208	299 (End of extension[2])
Month	Pivotal phase EOS + 6 months	0	3	6	9	12	15	18	21	24[2]
Obtain informed consent		X								
Pregnancy test in women[4]		X								X
Call IVRS/IWRS	X	X	X	X	X	X	X	X	X	X
Prior & Concomitant Antidiabetic & CVD Medications	X		X	X	X	X	X	X	X	X
Concomitant Medications	X	X[9,10]	X	X	X	X	X	X	X	X
AE (prompting for infections, malignancies, CV events)[11]	X	X[9,10]	X	X	X	X	X	X	X	X
Drug administration		X	X[8]	X	X	X	X	X	X	
Study phase completion form	X									X
EQ-5D[5]	X			X				X		X
Vitals (includes BMI, weight, waist circumference)	X			X				X		X
Physical Exam	X									
ECG	X									
hsCRP	X									
HbA1c & FPG	X[7]									
Standard Hematology & Chemistry	X									
Fasting Lipid Profile[6]	X									
Urinalysis including albumin/creatinine ratio	X									

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[1] Patients with prediabetic status as defined by HbA1c/FPG lab values of HbA1c of 5.7 – 6.4% or FPG of 100 – 125 mg/dL (= 5.6 – 6.9 mmol/L) at both pivotal phase randomization and pivotal phase EOS will participate in study drug washout before they restart study drug administration as part of the extension phase at visit 201 (Month 0), provided they sign the Informed Consent Form.

[2] The extension phase will continue in an individual country for a minimum of two years from the date of the first patients enrolled in that country. The maximum duration of the extension phase will be 2.5 years from the date of the first patient enrolled in that country or until marketed product is available in that country, whichever comes first.

[3] The first visit of the main drug dispensing period of the extension phase at Month 0 (Visit 201) should occur on the same day as the End of Prediabetes Washout visit (Visit 199). Prior & Concomitant Antidiabetic & CVD Medications, Concomitant Medications, Vitals and AE assessment are not required at visit Month 0 (Visit 201) if they are performed as part of the End of Prediabetes Washout visit (Visit 199).

[4] Mandatory for all women, regardless of menopause or surgical history. Urine pregnancy test to be performed locally.

[5] Please see Section 6.6.4 for administration of the questionnaire.

[6] Patient must have fasted 10 hours for this test. Triglycerides (TG), total cholesterol, HDL cholesterol, LDL cholesterol, VLDL cholesterol and non-HDL cholesterol. LDL Cholesterol, VLDL cholesterol and non-HDL cholesterol will be calculated unless triglycerides > 400 mg/dL in which case a direct LDL cholesterol assay will be employed.

[7] An unscheduled visit will be conducted within 6 weeks if no HbA1c value is available from the End of Prediabetes Washout visit (visit 199) or if a diabetes diagnosis is only based on one FPG value of ≥ 126 mg/dL (≥ 7 mmol/L) at the End of Prediabetes Washout visit.

[8] Visit 202 (Month 3) will be the first scheduled visit at which an open-label dose of 150 mg canakinumab will be administered. The intermediate dose of 150 mg canakinumab will be administered until the final dose of canakinumab is implemented at the study sites based on the results from the pivotal phase.

[9] Adverse Events and Concomitant Medications ongoing from the End of Prediabetes Washout visit must be re-entered into the extension phase visit Month 0 (Visit 201) Adverse Event eCRF and Concomitant Medication eCRF, respectively.

[10] Adverse Events and Concomitant Medications will be newly assessed for patients who do not have their End of Prediabetes Washout visit on the same day as the first visit of the main drug dispensing period of the extension phase.

[11] New medical histories must be added to the Adverse Event eCRF.

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6.1 Information to be collected on screening failures

All patients where informed consent has been given for the pivotal phase (including screening failures), will have the Screening Phase Disposition, Demographics, Inclusion / Exclusion, Informed Consent and Adverse Event (if SAE data has been collected) eCRFs completed.

For screened patients who signed informed consent but are not randomized or entered into the next period of the study (usually starting at visit 1) will have adverse events that are not SAEs followed by the investigator and collected only in the source data.

For all patients who signed the informed consent and are randomized, or who are entered into the next period of the study, will have all adverse events occurring after informed consent recorded on the Adverse Event eCRF page, with the exception of all study endpoints.

The investigator will have the discretion to record abnormal test findings on the Medical History eCRF whenever, in their judgment the test abnormality occurred prior to the informed consent signature. For example: an investigator can determine that an ECG abnormality that was seen on an ECG conducted after informed consent was obtained was a pre-existing condition. This pre-existing condition is then recorded on the Medical History eCRF and not as an adverse event.

6.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients include: information on date of birth (if allowable), age, sex, race and ethnicity.

Relevant medical history/current medical conditions present before signing informed consent will be collected at Visit 1 of the pivotal phase. General medical history will include: HEENT, Neoplastic and Hematological Disorders, Cardiovascular history, including MI history, prior events or disease, hypertension, hyperlipidemia, smoking history, Respiratory, Kidneys and Urinary Tract, Gastrointestinal, Immunological and infectious, Endocrine and Metabolic including history and diagnosis of diabetes and it's complications, CNS including psychiatric disorders. Relevant medical history/current medical condition data includes data until signing of informed consent. Where possible, diagnoses and not symptoms will be recorded. Family history for cardiovascular diseases will be collected.

6.3 Treatment exposure and compliance

Study treatment will be administered at the clinic under the supervision of the investigative staff with the dosing record captured within each visit on the Drug Accountability eCRF.

Any medications taken within 30 days prior to the date of screening and after will be recorded on the appropriate Concomitant Medications and or Procedures and Significant Non-drug Therapies eCRF.

This will also apply for the extension phase.

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6.4 Efficacy

6.4.1 Primary Efficacy assessment (primary objective)

The primary endpoint is defined as the time to the first adjudication committee confirmed major adverse cardiovascular event (MACE) occurring during the double-blind treatment period of the pivotal phase, which is a composite of CV death, non-fatal MI, and stroke.

An independent adjudication committee that is blinded to treatment assignments will review and adjudicate all clinical events that constitute the primary composite endpoint and secondary endpoints.

In the extension phase no endpoints will be collected. MACE will be recorded as adverse events, using the Adverse Event eCRF. No adjudication of events will be performed during the extension phase. Reporting of Adverse Events is described in Section 7.

6.4.2 Secondary efficacy assessment (secondary objectives)

All the listed secondary efficacy assessments are for the pivotal phase only unless specified otherwise. Key secondary efficacy assessments will comprise:

- Time to the first occurrence of the adjudication committee confirmed composite cardiovascular endpoint consisting of primary endpoint, and hospitalization for unstable angina requiring unplanned revascularization
- Time to adjudication committee confirmed new onset of type 2 diabetes among those with pre-diabetes at randomization (defined in Section 4) (time to NOD)

Other secondary efficacy assessments will comprise

- Time to first event of, non-fatal MI, stroke and all-cause mortality composite
- Time to all-cause mortality

Exploratory efficacy assessments will comprise

- Time to first event of total vascular events composite consisting of primary endpoint, hospitalization for unstable angina, or for any other non-coronary ischemic event (transient ischemic attack or limb ischemia), any revascularization procedure (coronary and non-coronary), coronary angiography and limb amputation
- Other cardiovascular disorders with a known inflammatory component:
    - Time to first deep vein thrombosis/pulmonary embolism
    - Time to first supraventricular tachycardia/atrial fibrillation
    - Time to first stent thrombosis (definite or probable)
    - Time to first hospitalization or prolongation of hospitalization for heart failure
    - Time to first major coronary event (CHD death or MI)
    - Time to first event of coronary revascularization procedures (PCI or CABG)
    - Time to first stroke by etiology
- Explore whether the early high, induction dose regimen in 300 mg canakinumab arm has an impact on early, within 90 days of randomization, primary and secondary clinical

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cardiovascular event when compared to 150 mg (and 50 mg) canakinumab arm with no early high, induction dose regimen.

- Glycemic control among those with type 2 diabetes at randomization (defined in Section 4)
  - HbA1c, FPG, and anti-diabetic medication changes by visit from baseline. This analysis includes both longitudinal as well as categorical assessments using HbA1c, FPG, and diabetic medication changes from baseline.
  - Failure of glycemic control analyses defined as HbA1c $\geq$ 7.5% (see Section 6.6.1)
  - Study drug washout in prediabetic patients: to assess the durability of any potential antidiabetic effect of canakinumab in prediabetic patients after discontinuation of study drug
- Change from baseline in biomarkers of cardiovascular and diabetes risk, including but not limited to nephropathy by albumin/creatinine ratio in patients with T2DM or pre-diabetes at baseline, inflammatory biomarkers, glycemic control markers, and β-cell function markers
- Change from baseline in patient reported outcomes of tiredness, physical function and performance function and in health status as assessed by the EQ-5D Quality of Life (QOL) assessment. EQ-5D: change from baseline for both pivotal phase and extension phase; in addition for extension phase, impact of treatment switch on EQ-5D
- Occurrence of events related to age-related macular degeneration (initial occurrence, worsening or need for treatment)
- Exploratory pharmacogenetic and pharmacogenomic assessments to examine whether individual genetic variation in genes relating to drug metabolism, major cardiovascular event, type 2 diabetes, and the drug target pathway confer differential response to canakinumab.

6.4.3 Appropriateness of efficacy assessments

Time to major adverse cardiovascular events and progression to diabetes (new onset diabetes) are well defined and standard clinical events in clinical trials aimed at demonstrating primary and secondary efficacy of investigational agents on clinical endpoints. Secondary endpoints are widely used clinical efficacy endpoints in cardiovascular clinical endpoint trials. Exploratory endpoints are hypothesis generating and exploratory in nature.

6.5 Safety

Safety and Tolerability Assessments

- Laboratory evaluations (performed during pivotal phase and prediabetes washout)
- Height, weight and waist circumference (performed throughout full study)
- Adverse events and serious adverse events, including cardiovascular events, malignancies, and infections (performed throughout full study)
- Discontinuation due to AEs (performed throughout full study)
- Hypoglycemia events (performed throughout full study)
- Injection site reactions (assessed throughout full study)
- Physical Exam (performed during pivotal phase and prediabetes washout)

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- Biomarkers (performed during pivotal phase)
- Vitals (assessed throughout full study)
- ECG (performed during pivotal phase and prediabetes washout)

Serious allergies/immunological events (e.g. Anti-canakinumab antibodies), serious infections, and malignancies adverse events will be monitored carefully using adverse/serious adverse events procedure described in Section 7.1 Adverse events and Section 7.2 Serious adverse event reporting during this trial because these adverse events represent hypothetical mechanism of action related risks of canakinumab therapy. During the pivotal phase, these adverse events will be adjudicated by an expert adjudication committee to strengthen data quality and safety conclusions. No adjudication of events will be performed during the extension phase.

6.5.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to signing of informed consent must be included in the relevant Medical History/Current Medical Conditions eCRF. Significant findings after the signing of informed consent, which meet the definition of an Adverse Event, must be recorded on the Adverse Event screen of the patient's eCRF.

Physical examination will also be performed during prediabetes washout but not during main drug dispensing period of the extension phase.

6.5.2 Vital signs

Vital signs including BP (3 measurements with the average of all three used for inclusion) and pulse measurements will be assessed per the assessment schedule. In general blood pressure should be taken after the patient has been sitting for five minutes, with back supported and both feet placed on the floor. Systolic and diastolic blood pressure should be measured three times using an automated validated device with an appropriately sized cuff. The repeat sitting measurements should be made at 1 to 2 minute intervals and the mean of the last three measurements will be used. If using the automated devise and current cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

Vital signs will also be performed during the extension phase.

Clinically notable vital signs are defined in Appendix 1.

6.5.3 Height, weight and waist circumference

Height in centimeters (cm) or inches and body weight (to the nearest 0.1 kilogram [kg] or pound [lb] in indoor clothing, but without shoes) will be measured. Body Mass Index (BMI) will be calculated as the weight in kg divided by the height in meters squared. Waist

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circumference should be measured with a flexible tape. For consistency among sites, the position for measuring waist circumference will be at the uppermost border of the right iliac crest (or at the umbilicus if landmarks cannot be palpated). The measure should be recorded while the patient is in the expiratory phase of respiration.

Height, weight and waist circumference will also be performed during the extension phase.

6.5.4 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual. All patients should be fasting for at least 10 hours prior to having the labs drawn at the scheduled time-points. All screening labs must be reviewed for completeness prior to randomization. Lab results that are missing or unavailable must be repeated prior to randomization.

Additional samples will be sent to the Central Laboratory for long term storage. Upon completion of the study these samples will be analyzed for cardiovascular and metabolic biomarkers and genetic analysis, if prior written informed consent is obtained.

Laboratory evaluations will also be performed during prediabetes washout but not during main drug dispensing period of the extension phase.

6.5.4.1 Hematology

The following tests are included in the hematology but are not limited to: HbA1c, Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count will be measured.

Hematology will also be assessed during prediabetes washout but not during main drug dispensing period of the extension phase.

6.5.4.2 Clinical chemistry

The following tests are included in the chemistry but are not limited to: hsCRP, eGFR, Estradiol, Fasting Plasma glucose, Blood urea nitrogen, creatinine, CK (CK-MB and troponin-I if CK is >2ULN and there is no underlying etiology for the increase in CK), total bilirubin, AST, ALT, alkaline phosphatase, sodium, potassium, chloride, calcium, phosphorous, total protein, albumin, and uric acid will be measured. FSH, HIV screen, HBsAg and HCV antibody will only be measured at Visit 1 for eligibility purposes.

Clinical chemistry will also be assessed during prediabetes washout but not during main drug dispensing period of the extension phase.

[For Japan only]

[In Japan, HBc antibody and HBs antibody will also be measured for Visit 1 eligibility purposes. This is not applicable for the extension phase.]

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6.5.4.2.1 Fasting Lipid profile

The following tests are included in the fasting lipid profile but are not limited to triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, VLDL cholesterol and non-HDL cholesterol. LDL cholesterol, VLDL cholesterol and non-HDL cholesterol will be calculated unless triglycerides > 400 mg/dL in which case only a direct LDL cholesterol assay will be employed.

Fasting Lipid profile will also be performed during the prediabetes washout but not during main drug dispensing period of the extension phase.

6.5.4.3 Urinalysis

Dipstick measurements for specific gravity, protein, glucose and blood will be performed. WBC and RBC sediments will also be measured as a reflex if the dipstick is abnormal. Dipstick will be performed by the central lab. The urine albumin/creatinine ratio will also be measured to assess the presence of micro- or macroalbuminuria in patients with T2DM or pre-diabetes at baseline.

Urinalysis will also be performed during the prediabetes washout but not during main drug dispensing period of the extension phase.

6.5.5 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed at baseline (Visit 2), yearly visits, and at the end of study visit. ECG's will be read by a central vendor. Each ECG tracing should be labeled with the study number, patient initials (if applicable), patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities should also be recorded on medical history/ adverse events eCRF page. Any potential endpoints should be recorded on the Clinical Study Endpoint Tracking Form eCRF.

ECG will also be performed during the prediabetes washout but not during main drug dispensing period of the extension phase.

6.5.6 Pregnancy and assessments of fertility

Neither the pivotal phase nor the extension phase include women of child bearing potential and therefore pregnancy test should be performed on all female study participants to detect unexpected pregnancies. A positive urine pregnancy test requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative. If the serum β-hCG is positive, the patient must be discontinued from study treatment but should continue follow up in the trial. Study treatment can be restarted after completion or termination of pregnancy following discussion with the Sponsor.

6.5.7 Appropriateness of safety measurements

Safety endpoints used in this trial are standard endpoints in demonstrating safety of investigational agents in clinical trials. Safety events of special interest, in the following categories, serious infections and malignancies, will be adjudicated by two expert adjudication committees during the pivotal phase. No adjudication of events will be performed during the extension phase. Additionally, canakinumab and canakinumab antibody

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concentrations will be measured during the pivotal phase due to the hypothetical risk of immune response to the study treatment. These safety events of special interest represent hypothetical risks of canakinumab treatment.

6.6 Other assessments

6.6.1 Assessment of durability of glycemic control for T2DM (exploratory endpoint)

These analyses are performed during the pivotal phase for patients with type 2 diabetes mellitus (T2DM) at randomization (defined in Section 4).

Patients with T2DM at randomization may be treated with any anti-diabetic medicine approved for use by local health authorities.

Long term glucose control durability of canakinumab will be assessed in patients with diabetes and HbA1c<7.0% at randomization by performing failure of glycemic control analysis. The first assessment of failure of glycemic control is at pivotal phase 6 month visit and thereafter every 6 months. Failure of glycemic control is defined as HbA1c $\geq$ 7.5% confirmed by a second HbA1c measurement within 6 weeks of the initial result. During this trial investigators should increase anti-diabetic medications or start new anti-diabetic medications only after HbA1c $\geq$ 7.5% has been confirmed in patients with diabetes and HbA1c<7.0% at randomization.

6.6.2 Assessment of durability of any potential antidiabetic effect in prediabetic patients following washout of study drug

Patients with prediabetic status at both randomization and the pivotal phase EOS visit will enter into a 6-month washout with no study drug administration at the beginning of the extension phase. Thus, patients will skip two doses of their pivotal phase blinded assigned treatment arm (Figure 3-3). Prediabetic status is defined by HbA1c of 5.7 – 6.4% or FPG of 100 – 125 mg/dL (= 5.6 – 6.9 mmol/L). The pivotal phase EOS glycemic status will be assessed based on the last HbA1c and FPG data available at the EOS visit. The purpose of this washout is to assess to what extent a potential lower incidence of diabetes diagnoses observed on canakinumab relative to placebo treatment during pivotal phase double-blind treatment is explained by a true delay in progression to diabetes as opposed to a lowering of FPG and HbA1c that masks diabetes but does not persist after the washout. Diabetes diagnosis will be based on HbA1c and FPG data as well as on any use of antidiabetic medications started during the washout period. An unscheduled visit will be conducted within 6 weeks if no HbA1c value is available from the End of Prediabetes Washout visit (Visit 199) or if a diabetes diagnosis is only based on one FPG value of $\geq$ 126 mg/dL ($\geq$ 7 mmol/L) at the End of Prediabetes Washout visit.

6.6.3 Healthcare Resource Utilization

Healthcare Resource utilization data will not be collected in this study.

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6.6.4 Patient Reported Outcomes

Patient reported outcomes (PRO) have been identified as important in the post MI patient population. While a variety of relevant concepts within the context of canakinumab have been identified, the concepts of tiredness, physical function and performance function have been selected as prioritized measurement concepts. In order to measure these concepts a set of PRO instruments will be administered.

The PRO instruments to be included in this pivotal phase, where available, are the SF-36, the Multidimensional Fatigue Symptom Inventory – Short Form (MFSI-SF) and the EQ-5D. Details on each of these instruments are provided in addition to the target population. The EQ-5D is the only PRO instrument that will also be performed during the extension phase, i.e. at the End of Prediabetes Washout visit, yearly during the extension phase and at the extension phase EOS visit.

For onsite visits only, it is strongly encouraged patients complete the questionnaire(s) before other clinical assessments.

Completed questionnaires will be reviewed and examined by the investigator before the clinical examination for responses, which may indicate potential AEs or SAEs. The investigator should review not only the responses to the questions in the questionnaires but also any unsolicited comments written by the patient

If the occurrence of AEs or SAEs is confirmed, the physician must record the events as per instructions given in Section 7.1 and Section 7.2 of the protocol. Investigators should not encourage the patients to change the responses reported in the PRO questionnaires

Patient Reported Outcome Measures

Baseline Post MI

1. **SF-36**

   Target population: Patients who are post MI 30 days to less than 6 months in US and pre-defined EU countries.

   The SF-36 has been selected to measure physical and performance function amongst patients post MI at several time points throughout the trial. The SF-36 is a 36 item measure developed by Cathy D. Sherbourne and John E. Ware. The SF-36 encompasses generic health concepts considered to be relevant across age groups, disease states and treatments types and has been validated in many disease states. For the purposes of this trial we will focus on the physical function and physical role domains, however the full instrument will be completed. The SF-36 will take patients approximately 5-10 minutes to complete. For this trial, the acute version of this measure, which includes a one week recall period, will be utilized.

   The SF-36 will be administered, where available, to patients enrolled in trial sites located in the U.S. and countries under the authority of the E.M.A. only. In addition, only patients who had a MI 30 days to less than 6 months of their enrollment date will be targeted for completing the SF-36. The SF-36 will be given to patients to complete in clinic as per the study assessment schedule.

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The SF-36 will not be assessed during the extension phase.

2. **MFSI-SF**

Target population: Patients who are post MI 30 days to less than 6 months in US and pre-defined EU countries.

The MFSI-SF is a 30 item measure developed by Danette Hann, Paul B. Jacobsen, and Kevin D. Stein. The MFSI-SF encompasses a wide spectrum of concepts related to fatigue including physical, mental and emotional tiredness. This instrument has a 7 day recall period and is expected to take approximately 5 minutes for patients to complete. This instrument has been selected to measure tiredness in patients post MI and post stroke at several time points throughout the trial.

The MFSI-SF will be administered, where available, to post MI patients enrolled in trial sites located in the U.S. and countries regulated under the authority of the E.M.A. only. In addition, only patients who had a MI 30 days to less than 6 months of their enrollment date will be targeted. The MFSI-SF will be given to patients to complete in clinic as per the study assessment schedule.

The MFSI-SF will not be assessed during the extension phase.

3. EQ-5D

Target population: All patients enrolled in the pivotal phase and all patients enrolled in the extension phase.

Generic multidimensional health-related quality of life will be assessed with the EuroQoL (EQ-5D). The EuroQol EQ-5D is a simple but effective standardized instrument designed for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides both a compact descriptive profile and a single index value that can be used in the clinical and economic evaluation of health care.

The EQ-5D measures five domains (mobility, self-care, usual activity, pain/discomfort & anxiety/depression).

There are two parts to this questionnaire. The first, ‘health state classification’ consists of five questions. The second, ‘Visual Analogue Scale Thermometer’ consists of a visual analogue scale. This generates a self-rating of current health-related quality of life. This will be used with the health state classification to build a composite picture of the respondent’s health status.

- Data capture

EQ-5D enables an accurate self-description of current health-related quality of life to be easily recorded. Self-explanatory instructions to respondents are provided within the questionnaire and it takes about two minutes to complete.

- Health State Classification

The first page consists of five questions. The respondent is asked to indicate his/her current health state, by ticking the most appropriate of three statements about each of the five quality of life dimensions.

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Each statement represents an increasing level of severity (1=no problem, 2=some or moderate problem, 3= unable or extreme problem). For example, a respondent with 'no problem' for each of the five questions will be said to have a health status of 11111.

- Visual Analogue Scale 'Thermometer'

The 'Thermometer' has end points of 100 (best imaginable health state) at the top and 0 (worst imaginable health status) at the bottom.

The respondent will rate his/her current health status by drawing a line from the box marked 'Your health status today' to the appropriate point on the 'thermometer' scale.

The site staff should record the two digit reading on the thermometer (where the line by the respondent crosses the thermometer) on the appropriate space in the CRF.

Missing or ambiguous values will be left blank.

Note: Questionnaire should be completed by the patient at the center, where available, before any other assessments take place.

6.6.5 Stroke Functional Assessment Sub-Study

Pre-clinical models indicate that anti-inflammatory therapy and specifically IL-1β blocking therapy may limit the size of stroke impact in brain tissue and facilitate functional recovery from stroke. Therefore, this clinical trial includes a sub-study on functional assessment of the patients recovering from stroke experienced during this trial and agreeing to participate in this sub-study in order to support the hypothesis that canakinumab therapy facilitates functional recovery from stroke.

The following 3 assessments will be performed on all patients who have suffered a stroke during the pivotal phase but not during the extension phase.

6.6.5.1 The Modified Rankin Scale

Performed 30 and 90 days post stroke during pivotal phase: The effects of canakinumab on patients who undergo an ischemic stroke during the pivotal study phase will be assessed using the Modified Rankin scale (mRS), which provides an assessment of overall global neurologic function through serial observation of a patient's ability to perform Activities of Daily Living (ADL). A diagnosis of ischemic stroke will be determined by usual Standard of Care, and will include neurologic signs and symptoms of ischemia accompanied by radiologic studies, which confirm the clinical diagnosis, as well as eliminating hemorrhagic stroke as a possible cause.

Patients will be examined at 30 and 90 days post-stroke by a Consulting Neurologist or if one is not available, a physician trained in mRS assessments, who will score the serial examinations as noted below. Day 90 post-stroke assessment will be the primary outcome of this sub-study.

Grade Description

0 No symptoms at all

1 No significant disability despite symptoms: able to carry out all usual duties and activities

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2 Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance
3 Moderate disability: requiring some help, but able to walk without assistance
4 Moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance
5 Severe disability: bedridden, incontinent, and requiring constant nursing care and attention
6 Death

The Modified Rankin scale will not be assessed during the extension phase.

6.6.5.2 MFSI-SF

Performed 30 and 90 days post stroke: Any patient who has a stroke at any time after enrollment in the trial will be targeted to complete the MFSI-SF instrument, where available, 30 days and at month 3 post their stroke event to assess tiredness. Any patient in the US or predetermined EU countries, who is to completing the MFSI-SF as a post MI patient and then has a stroke event (also recurrent stroke events) will also complete this questionnaire.

The MFSI-SF will not be assessed during the extension phase.

6.6.5.3 SIS-16

Performed 30 and 90 days post stroke: The SIS-16 has been selected to measure physical function and performance function in patients post stroke at several time points throughout the trial. The SIS-16 is a 16 item measure, which was developed by Pamela W. Duncan. The SIS-16 encompasses a spectrum of concepts for physical function and performance function specific to stroke. The instrument utilizes a 2 week recall period.

The SIS-16 will be administered, where available, at all trial sites to any patient who has a stroke occur at any time after enrollment as well recurrent stroke events. The SIS-16 will be given to patients to complete in clinic at 30 and 90 days post their stroke event.

The SIS-16 will not be assessed during the extension phase.

6.6.6 Macular Degeneration

Macular degeneration (also known as age-related macular degeneration (AMD)) will be assessed for by patient interview at the Screening Visit/Visit 1 and at visits every 6 months from baseline through the EOS visit of the pivotal phase. Patients will also be asked if they have had an injection in their eye at the Screening Visit/Visit 1 and at six-month intervals from baseline through the EOS visit of the pivotal phase. Information obtained from the patient interview will be reported in the patient source and in the database on the Macular Degeneration eCRF and in the medical history, adverse event and concomitant medication eCRFs as appropriate.

Macular degeneration will not be assessed during the extension phase.

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6.6.7 Pharmacokinetics

6.6.7.1 Blood collection

All blood samples must be taken at each indicated visit prior patient receiving their study medication injections. Blood samples will be taken at any time point by either direct venipuncture or an indwelling cannula inserted in a forearm vein.

For each scheduled PK sample, 2 mL of blood will be drawn into a plain barrier tube, to obtain 1.5 mL serum. The sample will be allowed to clot during 45 minutes at room temperature. The serum will be obtained by centrifugation at approximately 2500 g for 10 minutes. The sample will be split into **two** aliquots to be transferred into freezer-proof polypropylene screw-cap tubes. Serum tubes will be frozen within 90 min of venipuncture and kept at ≤ -18°C pending shipment on dry ice. One of the two serum samples is to be kept at the study site as a backup while the other one will be shipped to the central lab.

For a detailed description of blood sampling schema, please refer to the Blood Log in Appendix 2

Time points for collection during pivotal phase:

- Baseline (Month 0): pre-dose
- Month 12 (pre-dose)
- Month 24 (pre-dose)
- EOS (No study drug administration during EOS visit. Blood can be collected any time during this visit.)

During the extension phase no blood samples will be collected for pharmacokinetics.

6.6.7.2 Analytical method(s)

An ELISA method will be used for bioanalytical analysis of canakinumab in serum, with an anticipated lower limit of quantification (LLOQ) of 100 ng/ml. The detailed method description to assess canakinumab concentration will be described in the bioanalytical raw data of the study and in the respective Bioanalytical Data Report (BDR)

6.6.7.3 PK sample handling, labeling and shipment instructions

6.6.7.3.1 Sample labeling

The samples for the pharmacokinetic profile will be labeled as follows:

PK

Study Code: CACZ885M2301

Patient Number:

Sample Number:

Date / Study Day:

Required Time:

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Labels will be provided to the investigator.

For each shipment, the same procedure described in Section 6.6.7 PK sample handling, labeling and shipment instructions has to be followed.

6.6.8 Pharmacodynamics

Total IL-1β (sum of free and bound canakinumab) will be determined in serum.

Pharmacodynamic (PD) samples are to be collected at visits shown in Table 6-1. No PD samples will be collected during the extension phase.

6.6.8.1 Blood collection

All samples must be taken prior receiving their injections All blood samples will be taken, prior to dosing, by either direct venipuncture or an indwelling cannula inserted in a forearm vein.

For each scheduled PD sample, 3 mL of blood will be drawn into a plain barrier tube, to obtain 1.5 mL serum. The sample will be allowed to clot during 45 minutes at room temperature. The serum will be obtained by centrifugation at approximately 2500 g for 10 minutes. The sample will be split into two aliquots to be transferred into freezer-proof polypropylene screw-cap tubes. Serum tubes will be frozen within 90 min of venipuncture and kept at ≤ -18°C pending shipment on dry ice. One of the two serum samples is to be kept at the study site as a backup while the other one will be shipped to the central lab.

For a detailed description of blood sampling schema, please refer to the Blood Log in Appendix 2

Time points for collection during pivotal phase:

- Baseline (Month 0): (pre-dose)
- Month 12(pre-dose)
- Month 24 (pre-dose)
- End of study

PD parameters: Total IL-1β in serum, this being the sum of free and bound canakinumab; rate of IL-1 production, clearance, and its binding affinity to canakinumab.

6.6.8.2 Analytical method(s)

Total IL-1β will be analyzed in serum by means of a competitive ELISA assay, limit of quantification (LLOQ) at 1 pg/ml.

Details of the analytical methods to assess total IL-1β in serum will be described in the bioanalytical data report.

6.6.8.3 PD sample handling, labeling and shipment instructions

6.6.8.3.1 Sample labeling

The samples for the pharmacodynamic profile will be labeled as follows:

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PD

Study Code: CACZ885M2301

Patient Number:

Sample Number:

Date / Study Day:

Required Time:

Labels will be provided to the investigator.

For each shipment, the same procedure described in Section 6.6.7 PK sample handling, labeling and shipment instructions has to be followed.

6.6.9 Immunogenicity assessments

Anti- canakinumab antibodies concentrations will be assessed in serum.

Blood samples for Immunogenicity (IG) assessments are to be collected at visits shown in Table 6-1. No IG assessments will be performed during the extension phase.

6.6.9.1 Blood collection

For each scheduled IG sample, 1 mL of blood will be drawn into a plain barrier tube, to obtain 500 µL serum. The blood sample will be allowed to clot during 45 minutes at room temperature. The serum will be obtained by centrifugation at approximately 2500 g for 10 minutes. Serum tubes will be frozen within 90 minutes of venipuncture and kept at ≤ -18°C pending shipment on dry ice.

If anaphylactoid reactions occur after injection, two more samples (at the time of the event and 8 weeks later) need to be taken.

6.6.9.2 Immunogenicity sample handling, labeling and shipment instructions

6.6.9.2.1 Sample labeling

The samples for the IG profile will be labeled as follows:

Anti- canakinumab Detection

Study Code: CACZ885M2301

Patient Number:

Sample Number:

Date / Study Day:

Required Time:

Labels will be provided to the investigator.

For each shipment, the same procedure described in Section 6.6.7 PK sample handling, labeling and shipment instructions has to be followed including sending a back up sample.

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6.6.9.3 Analytical method(s)

Immunogenicity (IG) will be analyzed using a bridging ELISA method. Anti-ACZ885 antibodies are captured in solution by combination of biotinylated and ruthenium-labeled forms of ACZ885. Complex formation is subsequently detected by Electro Chemi Luminescence using a Mesoscale Discovery streptavidin plate.

Further characterization of positive samples will be conducted using an ELISA based neutralizing antibody assay. PK data are required for all immunogenicity sampling time points to interpret the data. The analyst will be unblinded in order to match PK data to immunogenicity data.

Details of the analytical methods to assess anti- canakinumab antibodies in serum will be described in the bioanalytical data report.

6.6.10 Pharmacogenetics/pharmacogenomics

In a predefined countries described in the laboratory manual, there is an optional pharmacogenetic and pharmacogenomic component which requires a separate signature if the patient agrees to participate. In participating countries, it is required as part of this protocol that the Investigator presents these options to the patient. Should a patient choose not to participate in the pharmacogenetics or pharmacogenomic sampling they may still continue into the trial.

Lab manuals will be provided with detailed information on country participation, sample collection, handling, and shipment. The sample collection date must be entered on the CRF (eCRF) page.

Any genetics sample that remains after analysis may be stored for up to 15 years to address scientific questions related to canakinumab, major cardiovascular event or type 2 diabetes.

No pharmacogenetic or pharmacogenomic sampling will be performed during the extension phase.

Pharmacogenetics

In a predefined countries described in the laboratory manual, exploratory pharmacogenetics research studies are planned as a part of this study with the objectives of identifying inherited genetic factors, which may (1) be related to major cardiovascular event, type 2 diabetes, hemostasis, inflammation, lipid, and/or coagulation disorders (2) predict response to treatment with canakinumab, or (3) predict genetic predisposition to side effects. We hope to develop a better understanding of major cardiovascular event and type 2 diabetes, and how patients respond to canakinumab.

Sample collection: One 10 mL blood sample will be collected at baseline (Visit 2) in an EDTA tube. After collection, the sample must be inverted several times to prevent clotting. If the blood draw at Visit 2 is missed, the sample should be taken at the next visit that a blood draw is already scheduled. Only one blood sample should be taken from the patient for this pharmacogenetic study. These samples will be shipped to the central lab.

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Pharmacogenomics

Pharmacogenomics studies will be done to identify gene expression (mRNA) patterns of blood cells that are associated with treatment response to canakinumab, or that possibly correlate with the severity or progression of disease.

Sample collection: Two 2.5 mL blood samples will be collected in PAXgene tubes at baseline, month 3 and month 12 visits. These samples will be shipped to the central lab.

6.6.11 Other biomarkers

Biomarker measurements will be obtained at randomization, Month 3, Month 12 and EOS in a subset of patients in predefined countries described in the laboratory manual. Additionally, in a subset of patients participating in the biomarker substudy as outlined in the laboratory manual, an additional blood collection will be obtained on an annual basis. A panel of biomarkers may include but are not limited to: IL-1Ra, IL-6, IL-18, leptin, adiponectin (total and high MW), TNFα, PAI-1 and fibrinogen.

Additional samples will be sent to the Central Laboratory for long term storage. Upon completion of the study these samples will be analyzed for cardiovascular and metabolic biomarkers

No other biomarkers will be assessed during the extension phase.

7 Safety monitoring

7.1 Adverse events

An adverse event is the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) occurring after signing informed consent.

Adverse events must be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria they induce clinical signs or symptoms, they are considered clinically significant or they require therapy.

The occurrence of adverse events should be sought by non-directive questioning of the patient during the screening process after signing informed consent and at each visit during the study

Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values, which are considered to be non-typical in patient with underlying disease

During the pivotal phase all adverse events, which are no protocol endpoints, must be recorded on the Adverse Events CRF with the below listed information. During the extension

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phase ALL adverse events must be recorded on the Adverse Events CRF with the following information:

1. the severity grade [mild, moderate, severe]
2. The relationship to the study treatment (Reasonable possibility that the AE is related: No, Yes)
3. Its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported at the time of the end of the study
4. whether it constitutes a serious adverse event (SAE)
5. the action taken regarding study treatment
6. whether medication or therapies taken (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
7. the outcome (not recovered/not resolved; recovered/resolved; recovered/resolved with sequelae; fatal; or unknown)

An SAE is defined as any adverse events (appearance of or worsening of any pre-existing condition, undesirable sign(s), symptom(s) or medical condition, which are not protocol endpoints, that meet the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
  - In CACZ885M2301, malignancies are considered medically significant. This classification will aid in the data collection on these events.

Study-specific adaption of the standard definition of AEs and SAEs

In order to avoid double reporting and unblinding of study endpoints, a study specific exemption has been granted from the Health Authorities not to report study endpoints as serious adverse events/adverse events in the pivotal phase. Therefore, any cardiovascular

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event sent for adjudication as a potential study endpoint or reported as a non-adjudicated cardiovascular endpoint by the investigator will not be reported as an adverse event /serious adverse event but will be captured on the Clinical Endpoint Form eCRF. Only if the adjudication committee determines that the event is not a study endpoint, will this event be reported as an adverse / serious adverse event following procedures described in Section 7.2 Serious adverse event reporting.

The study specific exemption does not apply to the extension phase. During the extension phase ALL adverse events will be reported as AEs following the procedures described in Section 7.1 and Section 7.2. No adjudication of events will take place during the extension phase.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 7.2.

All adverse events should be treated appropriately. Action taken may include one or more of the following: no action taken (i.e. further observation only); study drug dosage temporarily interrupted; study drug permanently discontinued; concomitant medication given; non-drug therapy given. The action taken to treat the adverse event should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent. - Assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, suspected relationship to the study treatment, interventions required to treat it, and outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

The investigator should also instruct each patient to report any new Adverse Experiences (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information should be recorded in the investigator's source documents, and if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse event reporting

To ensure patient safety, every SAE, regardless of suspected causality, except for those being adjudicated as endpoints or are reported as non-adjudicated cardiovascular endpoint by the investigator during the pivotal phase, which occur after the patient has provided informed consent and until 90 days after the last study visit (following the last administration of study treatment if there are post-treatment follow-up visits) must be reported to Novartis within 24 hours of learning of the occurrence. Any SAEs experienced after this 90 day period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug.

Hypoglycemia events, which require hospitalization or the assistance of another person to treat must, be reported as an SAE.

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Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to study drug(s), complete the SAE Report Form in English and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Reporting of events (including coincidental cardiovascular events) that are both study endpoints and AE's / SAE during pivotal phase

The integrity of the pivotal phase may be compromised if cardiovascular events that are study endpoints are systematically unblinded in order to fulfill European SUSAR reporting requirements for SAE (European Commission ENTR/CT12 Guideline (2006)). Therefore, in the pivotal phase, potential study endpoints are excluded from the definition of AE's and SAE's and are not to be captured as AE and SAE's but only on the relevant study endpoint CRF. During the pivotal phase, these events are therefore NOT to be reported to Novartis within 24 hours on SAE forms and will not be reported to regulatory agencies or investigators other than as a study endpoint in the Clinical Study Report. Reporting to IRB's should follow local guidelines.

The following pre-defined study endpoints are excluded from the definition of AEs and SAE's in the pivotal phase:

- CV and non-CV Deaths (please see section Reporting of Deaths for specific exceptions for selected non-CV deaths that must be reported as both endpoints AND SAEs)
- Fatal and non-fatal MI
- Fatal and non-fatal Stroke (e.g. hemorrhagic stroke, ischemic stroke)
- Unstable angina requiring unplanned coronary revascularization
- Stent Thrombosis (per ARC definition)
- Hospitalization or prolongation of hospitalization for heart failure
- Critical Limb ischemia

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- Limb amputation
- Transient Ischemia Attack (TIA)
- New onset type 2 diabetes (NOD)
- Non-Coronary revascularization procedures
- Coronary angiography / Coronary Revascularization (PCI or CABG)
- Atrial fibrillation/ atrial flutter/ supraventricular tachycardia
- Pulmonary embolism and deep vein thrombosis

The Data Monitoring Committee (DMC) will review these endpoint data throughout the pivotal phase in an unblinded manner. Should the DMC make recommendations on the conduct of the pivotal phase that are considered to have significant bearing on the benefit risk of the trial, these will be communicated to competent authorities, IRBs/IECs and investigators and the ECs by Novartis in an appropriate timescale.

Any event that is not listed under the pre-specified endpoints above should be reported as an SAE. If it meets SUSAR criteria, the event will be unblinded; a report to competent authorities and relevant ethics committees and issuance of an IND Investigator Safety Letter will occur per local regulatory requirements.

Should an investigator during the pivotal phase consider that the character and the severity of the above listed events is not consistent with the expected presentation or course of that endpoint and the investigator considers that the study drug may have contributed to this abnormal presentation, then this event should be reported as an SAE and an endpoint.

Should an investigator report an SAE during the pivotal phase that is considered by Novartis to be potentially consistent with a study endpoint, Novartis will request confirmation from the investigator that this event is indeed an SAE and not an endpoint. The investigator should respond immediately to these requests in order to minimize the risk that such an event may require unblinding for regulatory reporting of SUSARs. Should the investigator, following this request for review, consider the event to be an endpoint the event must be included as an endpoint and confirmation sent to Novartis DS&E that the event should no longer be considered an SAE. Should the investigator either fail to reply in the necessary timeframe, or confirm that the event is an SAE and not an endpoint, the event will be handled as an SAE.

Events that following data review and adjudication are deemed not to be endpoints for this study will be reported as AEs and SAEs, as soon as adjudication process has been completed, following standard reporting guidelines.

During the extension phase, endpoints will no longer be collected. The above described protocol exemption does not apply for the extension phase. During the extension phase ALL SAEs must be reported to Novartis within 24 hours of learning of the occurrence as outlined in Section 7.2.

[For Japan only]

[In Japan, the following pre-defined study endpoints must be reported to Novartis Pharma K.K within 24 hours of learning of the occurrence, using the “Japan Pre-defined Study

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Endpoints Reporting Form". The detail of cases that need to be reported to Novartis Pharma K.K. and procedures for reporting are described in a separate document.

- Stent Thrombosis (per ARC definition)
- Hospitalization or prolongation of hospitalization for heart failure
- Critical Limb ischemia
- Limb amputation
- Transient Ischemia Attack (TIA)
- New onset type 2 diabetes (NOD)
- Non-Coronary revascularization procedures
- Coronary angiography / Coronary Revascularization (PCI or CABG)
- Atrial fibrillation/ atrial flutter/ supraventricular tachycardia
- Pulmonary embolism and deep vein thrombosis

This will not apply to the extension phase.]

Reporting of deaths

It is important to note that ALL deaths (deaths considered by the investigator to be CV and non-CV causes) must be reported as predefined study endpoints during the pivotal phase and the investigator must send all documentation for adjudication.

The following SAEs have been causally associated with non-CV deaths due to various medications in the past. Therefore, if a patient during the pivotal phase, is considered to have died as a result of any of the following events, the death must be reported as both an endpoint AND as SAE. The SAE must be reported to Novartis as per SAE reporting guidelines.

NON-CV FATAL EVENTS THAT ARE REPORTED AS BOTH DEATH ENDPOINTS AND SAEs DURING PIVOTAL PHASE

- Allergy events: Anaphylaxis, Angioedema, Laryngeal edema
- Serious hepatic events including hepatic failure, hepatic necrosis, Hy's law case, acute yellow liver atrophy
- Serious cutaneous skin reactions including: Stevens-Johnson syndrome, Toxic epidermal necrolysis, Erythema multiforme
- Drug induced hematological syndromes (including agranulocytosis, aplastic anemia, bone marrow failure, pancytopenia and bicytopenia)
- Inflammatory lung disorders (including allergic, fibrosing, and necrotising alveolitis, eosinophilic pneumonia and interstitial lung disease)
- Autoimmune myocarditis
- Suicide including drug overdose
- Malignant hypertension
- Pulmonary hypertension
- Renal failure (acute and chronic) including tubulointerstitial nephritis
- Hyperpyrexia, Hyperthermia malignant

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- Opportunistic infections
- Systemic lupus erythematosus
- Hypoglycemia
- Torsade de pointes, Long QT syndrome
- Pancreatitis
- Drug interaction
- Rhabdomyolysis
- Seizure
- Guillain-Barre syndrome
- Progressive multifocal leukoencephalopathy (PML)

In case the cause of the death event is not listed above it will be reported as study endpoint only. If the death event is adjudicated as a non-CV death, the death event will be reported as serious adverse event.

Reporting of adverse events during extension phase

During the extension phase, endpoints will no longer be collected. The above described protocol exemption does not apply for the extension phase. Therefore ALL adverse events are collected as SAE's, as described in Section 7.2. During the extension phase ALL SAEs must be reported to Novartis within 24 hours of learning of the occurrence.

7.3 Reporting of study treatment errors including misuse/abuse

This section applies to the extension phase only.

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (European Medicines Agency (EMA) definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the DAR (dose administration record) eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE.

Treatment error type	Document in Dose Administration (DAR) eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE

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Treatment error type	Document in Dose Administration (DAR) eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Misuse/Abuse	Yes	Yes,	Yes, even if not associated with a SAE

7.4 Pregnancies

Women of child-bearing potential are excluded from this study (pivotal and the extension phases); however, in the event a woman became pregnant we must ensure patient safety. Each pregnancy in a patient on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

7.5 Data Monitoring Committee

An external and independent DMC will be formed for the pivotal phase to periodically review safety information, and to evaluate the interim results relative to pre-defined statistical criteria to see if the trial has reached standards allowing stopping for proof of efficacy or for futility.

The DMC will include experts in cardiovascular and cerebrovascular disease, T2DM, large scale clinical trials and statistics; the members will review the results confidentially and will have no other roles in the study.

The membership of the DMC and the responsibilities of the DMC and Novartis will be defined in a separate document entitled the "Data Monitoring Committee Charter." The DMC Charter will include information about the data flow, purpose, timing of DMC meetings, guidance in the decision-making process, communication strategy, procedures for ensuring confidentiality, procedures to address conflicts of interest, and statistical monitoring guidelines.

For the extension phase the DMC will not be utilized.

7.6 Adjudication Committees

There will be three separate adjudication committees for the pivotal phase. There will be no adjudication committees utilized for the extension phase.

7.6.1 Cardiovascular clinical events adjudication committee

During the pivotal phase, cardiovascular clinical events will be adjudicated under blind by an adjudication committee, composed of reviewers who are experts on cardiovascular and cerebrovascular disease and T2DM. This measure is designed to ensure the objectivity,

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reliability and validity of the event classification. The procedures for reporting and case definitions are detailed in a separate charter document. The following primary and secondary endpoints will be adjudicated:

- All death
- Non fatal MI
- Stroke (e.g. hemorrhagic stroke, ischemic stroke)
- Unstable angina requiring unplanned coronary revascularization
- New onset type 2 diabetes mellitus

Definitions of clinical endpoints are described in Appendix 3.

The primary endpoint will be assessed based on MACE adjudicated to have occurred between a patient's randomization and either

1. the patient's entry into the prediabetes drug washout period,
2. or the patient's entry into the main drug dispensing period of the extension phase,
3. or for those patients not proceeding to neither prediabetes washout nor the main drug dispensing period of the extension phase, the patient's pivotal phase end of study visit, but only if it occurred during the pivotal close-out period,
4. or otherwise the end of the pivotal close-out period (analysis cut-off).

Thus, events occurring after informed consent but before randomization do not need to be adjudicated and should instead be reported as adverse or serious adverse events. Events occurring in the extension phase (including the prediabetes washout) should be reported as adverse events, as specified in Section 7.1 and Section 7.2.

Baseline and yearly ECG will be obtained during pivotal phase to assess interval ECG changes for study patients. Myocardial infarctions detected as interval ECG changes without clinical sequelae ("silent myocardial infarction") will be reported as endpoint. Interpretation of all scheduled ECGs will be done by a central ECG vendor (eRT, Philadelphia, PA) using qualified expert physicians.

The diagnosis New MI should be used when an ECG shows an MI that was not present on previous ECGs for the study patient. Previous ECGs must be available. This diagnosis should be used the first time the new MI is seen, but not for subsequent ECGs.

All unplanned hospitalizations except those related to planned procedures that are non-CV related will be reviewed for adjudication and adjudicated when data allows adjudication.

No cardiovascular clinical events adjudication committee will be utilized for the extension phase.

7.6.2 Infection Adjudication Committee

An independent Infection Adjudication Committee (IAC) has been formed on a program level and will review pertinent data from this pivotal trial.

The mission of the IAC is to independently and blindly review, evaluate and categorize new reports of pre-defined infections as they become available during the conduct of this trial. Members from the IAC may also adjudicate reports of serious allergies.

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The members, detailed mission and procedures of the IAC are detailed in the IAC charter.

The IAC will not adjudicate cases from the extension phase.

7.6.3 Malignancy Adjudication Committee

An independent Malignancy Adjudication Committee (MAC) has been formed on a program level and will review pertinent data from this trial.

The mission of the MAC is to independently and blindly review, evaluate and categorize reports of malignancy events across all potential indications and therapeutic areas in the canakinumab development program. Members from the MAC may also adjudicate reports of serious allergies.

The members, detailed mission and procedures of the MAC are detailed in the MAC Charter.

The MAC will not adjudicate cases from the extension phase.

8 Data review and database management

8.1 Site monitoring

Before pivotal phase initiation, at an investigator's meeting and/or a site initiation visit, a Novartis or study team representative will review the protocol and (e)CRFs with the investigators and their staff. This review will not be repeated for the extension phase. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the (e)CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyse data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on (e)CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the (e)CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the (e)CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

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8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Oracle Clinical/Remote Data Capture (OC/RDC) system. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify on a regular basis that the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data (either paper or CD-ROM) for archiving at the investigational site.

This will also apply for the extension phase.

The pivotal phase data and the extension phase data will be collected in two separate databases in order to avoid any risk of unblinding of pivotal phase data and in order to guarantee a secure pivotal phase database lock while the extension phase is ongoing. The name of the extension phase database and of some extension phase related documents will contain an identifier added to the study number CACZ885M2301.

8.3 Database management and quality control

Novartis staff review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff who will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO). Beyond the assessments during the study drug washout in prediabetic patients, no laboratory samples will be generated during the extension phase.

ECG readings will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO). Beyond the assessments during the study drug washout in prediabetic patients, no ECG will be generated during the extension phase.

Randomization codes and data about all study drug dispensed to the patient will be tracked using an Interactive Voice Response System (IVRS/IWRS). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

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The occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete for the pivotal phase (i.e. excluding the extension phase with the study drug washout in prediabetic patients, which will be reported separately) and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the Clinical Science Unit Head and the IIS Program Head.

Each occurrence of a code break via IVRS/IWRS will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.This will also apply for the extension phase until patients switch to the open-label canakinumab dose.

Pharmacogenetic/Pharmacogenomic samples:

To maximize confidentiality, all samples and the information associated with the samples will be double-coded to prevent the exposure of the patient's information and identity. This double-coding process allows the destruction of the sample at the patient's request. In addition, sample information is stored in one secured database while genetic data is stored in an independent secured database.

The use of pharmacogenetics to search for biomarkers of disease and drug action is exploratory. Any results from this pharmacogenetic study will not be placed in the patient's medical records.

No pharmacogenetic or pharmagenomic samples will be generated during the extension phase.

9 Data analysis

9.1 Analysis sets

The following analysis populations will be defined for statistical analysis:

- **Screened set** – All patients who signed the informed consent.
- **Randomized set** – All patients who received a randomization number, regardless of receiving trial medication.
- **Safety set (SAF)** – All patients who received at least one dose of study treatment and have at least one post-baseline safety assessment. Of note, the statement that a patient had no adverse events also constitutes a safety assessment. Patients will be analyzed according to treatment received. Treatment received will be considered identical to the randomized treatment if the patient has during at least one visit received at least one (of the two) injections constituting the treatment assignment at randomization and no wrongly administered injections constituting a different treatment group.
- **Full analysis set (FAS)** – All randomized patients. This is the primary efficacy population applied in all efficacy endpoints. Following the intent-to-treat principle, patients are analyzed according to the treatment they have been assigned to at the randomization. However, patients who have not been qualified for randomization and who have been inadvertently randomized into the study are excluded from FAS, provided these patients have not received study treatment.

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- **Per protocol set (PPS)** – a subset of the FAS, consists of all randomized patients in FAS who take at least one dose of study medication and have no major protocol deviations affecting the primary endpoint analyses. Major protocol deviations leading to exclusion from PPS will be specified prior to database lock on a blinded basis and documented in a separate document.

Note: The last part of the definition of the FAS is what is often referred to as misrandomized patients; i.e. patients for whom IVRS/IWRS calls were made by the site either prematurely or inappropriately prior to confirmation of the patient's final randomization eligibility and double-blind medication was not administered to the patient. These patients would subsequently not continue to take part in the study or be followed-up. Misrandomized patients will not be included in the FAS, but they will be included in the Randomized Set. Further exclusions from the FAS may only be justified in exceptional circumstances.

Analyses will take into account the changes in randomization between trial part 1 and trial part 2 (e.g. by stratifying analyses by trial part) and that patients in trial part 2 were not recruited concurrently with those in trial part 1. This ensure no biases arise e.g. due to differences over time (and thus between the two trial parts) in the recruited patient population or background medical care. Unless otherwise specified, patients randomized to the same treatment arm under randomization plan A or B will be analyzed together. This is not believed to introduce any biases with respect to the assessment of endpoints and the standard or care provided to patients, because patients have an equal 2:1 chance of being on an active treatment group under either randomization plan. Thus, it is not considered necessary to also stratify analyses in this respect.

9.2 Patient demographics and other baseline characteristics

The number of patients screened, randomized and included in FAS will be presented by treatment group and overall for the screened set, as well as by trial part. In addition, the reasons of screen failures will be provided for screened set as well. The number and percentage of patients in the randomized set who completed the study, who discontinued the study and the reason for discontinuation will be presented for each treatment group and all patients, as well as by trial part. The frequency (%) of patients with major protocol deviations as well as the criteria leading to analysis sets will be presented in separate tables for the randomized set. Finally, the number of enrolled and randomized patients by region as well as the number of patients enrolled and randomized per region and country will be presented descriptively for the randomized set overall and by trial part.

Baseline value is defined as the last non-missing assessment prior to the first dose of randomized study medication unless specified otherwise.

The following common background and demographic variables will be summarized by trial part using descriptive summary statistics (for continuous variables mean, median, standard deviation, Q1 (25th percentile), Q3 (75th percentile), minimum and maximum and for categorical variables frequency and percentage):

- Age [years]
- Sex
- Race

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- Ethnicity
- Height [cm]
- Weight [kg]
- Body mass index [kg/m^2] calculated as weight [kg]/ height^2 [m^2]
- Waist circumference [cm]
- Sitting pulse [bpm]
- Mean sitting SBP [mmHg]
- Mean sitting DBP [mmHg]
- Smoking history
- Alcohol history
- Region (Country) of enrollment
- Cardiovascular risk factors and other co-morbidities including but not limited to following:
  - Diabetes mellitus, complications of diabetes
  - Hypertension
  - Dyslipidemia/Hyperlipidemia
  - Atrial fibrillation
  - Supraventricular tachycardia
  - Deep Vein Thrombosis
  - Pulmonary embolism
  - Prior repeated MI (multiple MIs in medical history)
  - Prior PCI
  - Prior stent implantation (incl. drug eluding stent or bare metal stent)
  - Prior CABG
  - Prior TIA/stroke
  - Congestive heart failure
- Medical history of gout
- Post MI index group
- hsCRP [mg/L (two values available with the mean of these two used in analysis)]
- HbA1c [%]
- FPG [mmol/L]
- Lipid profile
- Glycemic status: T2DM, pre-diabetes, normoglycemic
- Level of exercise
- Family history of MI, stroke or diabetes
- Highest degree of education

Treatment group comparability will be examined using the Cochran-Mantel-Haenszel test stratified by trial part and time since index MI for the categorical variables and the F-test for the continuous variables as appropriate. These p-values will be provided for descriptive

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purposes and will not be considered to define any formal basis for determining factors that should be included in statistical models. If imbalances between treatment groups with respect to some variables occur, additional supplemental analyses may be performed to assess the impact of these imbalances as appropriate.

9.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

Study drug

The duration of the randomized treatment received during the double-blind pivotal phase will be computed as the time from the first injection to the first out of

1. the last injection date plus a quarter year (91 days),
2. the patient's death
3. or the patient's pivotal phase completion visit during the pivotal phase close-out period.

This algorithm reflects the planned treatment schedule and the long half-life of the study drug. The duration of the treatment period will be summarized for the full analysis set and safety set by trial part and treatment group descriptively including by duration categories. The overall patient-years of treatment will be computed as the sum of patient years of double-blind treatment for all patients.

Duration of exposure to study treatment excluding interruptions will be computed and summarized as above, but not counting periods during which the last injection was more than a quarter year ago.

Prior and concomitant therapies

Prior or concomitant medications will be summarized for the safety set and full analysis set in separate tabulations by trial part based on the coding dictionary used. Medications will be presented in alphabetical order, by preferred terms and grouped by anatomical main group. Tables will show the overall number and percent of patients receiving at least one drug of a particular preferred term and at least one drug in a particular anatomical main group.

Prior medications and significant non-drug therapies are defined as any medications and significant non-drug therapies taken prior to the randomization visit. Concomitant medications and significant non-drug therapies are defined as those used during the double-blind period. Concomitant medications that were prohibited as per protocol and given during the conduct of the study as well as significant non-drug therapies will be summarized.

Furthermore, the following classes of medications to be precisely defined in the statistical analysis plan, at time of randomization and during the double-blind period, which are relevant to program indication, will be summarized separately:

- Anti-ischemic agents
    - Beta blockers
    - Intravenous or oral nitrates
    - Calcium channel blockers

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- Anti-platelet agents
  - Acetylsalicylic acid (aspirin)
  - Non-aspirin oral anti-platelet agents (like P2Y12 inhibitors clopidogrel and prasugrel)
- ACE inhibitors (like ramipril)
- ARBs
- Lipid-lowering agents
  - Statins
  - Non-statins (like fibrates, binding resins and nicotinic acid)
- Diuretics
  - Thiazide diuretics
- Anti-diabetic medications
  - Insulin
  - Thiazolidinediones
  - Other oral hypoglycemic agents
- Proton pump inhibitors
- Anticoagulants

9.4 Analysis of the primary variable(s)

The primary analysis and all analyses of secondary/exploratory endpoints will use the Full Analysis Set (FAS), which reflects the intention-to-treat principle.

Unless otherwise specified all time-to-event analyses will be based on events occurring during the double-blind period of the pivotal phase. This means that only events between a patient's randomization and the first of either

1. the patient's entry into the prediabetes washout period for prediabetic patients,
2. or the patient's entry into the main drug dispensing period of the extension phase,
3. or for those patients proceeding to neither washout nor main drug dispensing period of the extension phase, the patient's end of pivotal phase visit, but only if it occurred during the pivotal phase close-out period,
4. or otherwise the end of the pivotal phase close-out period (analysis cut-off) will be counted in these analyses.

9.4.1 Variable

The primary efficacy variable is the time to first occurrence of a major adverse cardiovascular event (MACE), which is a composite endpoint consisting of cardiovascular death, non-fatal MI, and stroke. An independent adjudication committee will review and adjudicate all clinical events that constitute the composite of the primary endpoints on a blinded basis.

The time-to-event is computed as the number of days from randomization to the onset of the primary endpoint event in the pivotal phase. Data on patients who do not reach the primary endpoint by the study end date will be censored at the latest date they are known to be at risk in the pivotal phase.

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9.4.2 Statistical model, hypothesis, and method of analysis

The primary statistical null hypotheses are

- H_{11}: The hazard rate of first adjudication committee confirmed MACE in the canakinumab 300 mg dose group is greater than or equal to the hazard rate of the placebo group
- H_{21}: The hazard rate of first adjudication committee confirmed MACE in the canakinumab 150 mg dose group is greater than or equal to the hazard rate of the placebo group
- H_{31}: The hazard rate of first adjudication committee confirmed MACE in the canakinumab 50 mg dose group is greater than or equal to the hazard rate of the placebo group.

Each null hypothesis is tested against the one-sided alternative that the hazard rate is smaller for the respective active dose group than for the placebo group.

These hypotheses will be tested by comparing each dose to placebo with a log-rank test stratified by time since index MI (30 days to < 6 months and ≥ 6 months) and by trial part using exact method for handling ties on the full analysis set (FAS) according to the intent-to-treat principle. The stratification according to trial part entails some statistical inefficiency compared to a trial that would have had 4 treatment groups from the start, especially for the 50 mg dose. However, this approach ensures that no biases arise e.g. due to differences over time between the two trial parts in the recruited patient population or background medical care. While investigators are not blinded to the assignment of patients to randomization plan A or B, this is not believed to introduce any biases with respect to the assessment of the primary endpoint and the standard or care provided to patients, because patients have an equal chance of being on an active treatment group under either randomization plan. Thus, it was not considered necessary to also stratify the analysis in this respect, but a sensitivity analysis will be conducted. A sensitivity with respect to the consistency of treatment effects in the two parts of the trial will also be performed.

The family-wise error rate will be controlled at the two interim analyses and the final analysis using the closed testing procedure shown in Figure 9-1 using the graphical method of Bretz et al. (Bretz, et al. 2009); however, in intersection null hypotheses involving the primary null hypotheses for the 300 mg, 150 mg or 50 mg doses these primary null hypotheses will be tested using a weighted version of Dunnett's test (Dunnett 1955). Specifically this means that for any intersection hypothesis from the full closure that contains at least two of H_{11}, H_{21} and H_{31}, a weighted Dunnett test amongst the primary null hypotheses is performed with the overall significance level for that test and the weighting chosen according to the weights assigned to these null hypotheses by the update algorithm of the graphical method. The nominal adjusted significance levels based on the weighted Dunnett test are always slightly larger than the corresponding Bonferroni levels would be. For example the mvtnorm package in R (Genz and Bretz 2009) calculates the nominal Dunnett significance levels at the final analysis for the 300 mg, 150 mg and 50 mg doses versus placebo in the test of the global null hypothesis to be 0.5500504%, 1.1001008% and 1.1001008%, respectively, as compared to Bonferroni levels of 0.49%, 0.98% and 0.98%. If other non-primary null hypotheses in such an intersection hypothesis have non-zero weight on the basis of Figure 9-1, the intersection null hypothesis will be rejected if either (a) these other null hypotheses can be rejected at a Bonferroni significance level based on that weight or (b) the primary null hypotheses can be rejected based on the weighted Dunnett test. All other intersection hypotheses are tested with

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a weighted Bonferroni test. Protection of the family–wise error rate at level alpha is still guaranteed when the transition weights on the directed edges are chosen as in Figure 9-1 (see comment below) and all the tests on secondary variables are performed at the level resulting from the graphical procedure. The consonance of the test procedure (Brannath and Bretz 2010) has also been ensured as described below.

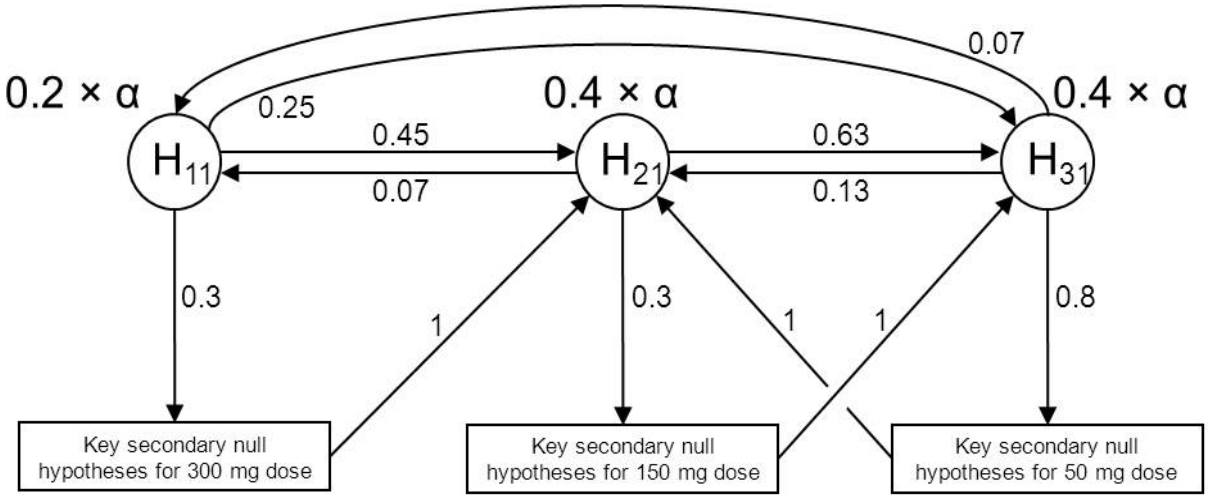
The testing procedure in Figure 9-1 initially splits the entire available significance level (at the final analysis 2.45%) between the three primary null hypotheses relating to the three doses (at the final analysis 20% of 2.45% = 0.49% for the primary null hypothesis of the 300 mg dose, 40% of 2.45% = 0.98% for that of the 150 mg dose and 40% of 2.45% = 0.98% for that of the 50 mg dose). These weights were chosen by balancing the prior expectations about the efficacy dose response relationship versus the potential for a better risk benefit ratio with lower doses. In particular, one aim was to ensure that there would be at least 80% power for the 50 mg dose to become significant assuming a 20% relative risk reduction for all doses. In the process of ensuring this, the weight for the 300 mg dose was reduced more than that of the 150 mg, because a higher dose is only of interest if it demonstrates a better efficacy than lower doses. This means that when the other doses are not effective the 300 mg dose would only become significant with a relative risk reduction that is at least in the region of 17.5%, while for the 150 mg dose this would already be the case with relative risk reductions below 16%. However, this was considered acceptable in order to ensure the desired operating characteristics for the 150 mg and 50 mg dose.

Key secondary endpoints for a dose are tested using a weighted Bonferroni-Holm procedure (Holm 1979) only after successful rejection of the primary null hypothesis for that dose. In that case, a higher fraction of the local significance level that is passed from the primary null hypothesis for a dose to the key secondary endpoints for the same dose is assigned to the secondary CV composite endpoint (90%) than to the new onset of diabetes endpoint (10%).

Note that if the primary endpoint for the 300 mg dose (null hypothesis H_{11}) is rejected 45% of the local significance level assigned to that null hypothesis is shifted to the primary endpoint for the 150 mg dose (null hypothesis H_{21}) and 25% to the primary endpoint for the 50 mg dose (null hypothesis H_{31}). This reflects the possibility that lower doses could potentially have a better safety profile than higher doses; hence, it would be desirable to demonstrate the efficacy of lower doses even after demonstrating the efficacy of a higher dose. In contrast, the main reason why some of the local significance level assigned to lower doses is shifted to higher doses is to preserve the consonance of the test procedure; i.e. to avoid a situation in which e.g. the primary null hypothesis for the 300 mg would be rejected by the weighted Dunnett test, but could not be rejected by the chosen closed testing procedure due to insufficient alpha being assigned to some intersection null hypotheses.

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Figure 9-1 Closed testing procedure for primary and key secondary endpoints



When the primary null hypothesis for a dose is rejected, some of the local significance level assigned to that primary null hypothesis is passed to the key secondary null hypotheses for the same dose. These are then tested using a weighted Bonferroni-Holm procedure at the available local significance level with weights of 90% for the key secondary CV composite and 10% for the key secondary new onset of diabetes endpoint. Only if both key secondary null hypotheses for a dose are rejected, will any of the local significance level assigned to these null hypotheses be passed on to null hypotheses for other doses.

Two efficacy interim analyses, at which the trial could be stopped for demonstrated efficacy or one or both active arms could be stopped for futility will be performed respectively after 50% and 75% of the target number of 1,400 patients have experienced a primary endpoint. Futility criteria and the criteria other than purely formal statistical significance required for stopping the trial for demonstrated efficacy will be specified in the Data Monitoring Committee charter. An additional futility analysis may also be conducted by the DMC prior to the first planned efficacy IA (at approximately 50% primary events), but only after a sufficient number of primary events are accrued, i.e, >25%.

A fixed Bonferroni split of the one sided significance level will be used to account for the two efficacy interim analyses and the final analysis, with a significance level of 0.01% for the first and 0.04% for the second efficacy interim analysis. I.e. the closed testing procedure will be performed with a one-sided significance level of 0.01% at the first efficacy interim analysis, with a one-sided significance level of 0.04% at the second efficacy interim analysis and with a one-sided significance level of 2.45% at the final analysis. In this fashion the familywise type I error rate will be controlled at the overall (one-sided) significance level $\alpha = 2.5\%$. This constitutes an equivalent level of evidence as the two-sided 5% level. Multiplicity adjusted p-values will be calculated for each null hypothesis as the smallest significance level at which one can reject that null hypothesis. Both one-sided and two-sided p-values will be reported. To obtain the latter, the same test procedure as shown in Figure 9-1 will also be conducted in a one-sided fashion on the 2.5% significance level to test for the superiority of placebo over each test arm.

The hazard ratios and their associated confidence intervals will be estimated by means of a (Cox 1972) proportional-hazards model stratified by time since index MI (< 6 months, ≥ 6 months) and by trial part using treatment (canakinumab doses and placebo) as a factor in the model using exact method for handling ties. Kaplan-Meier type plots will be presented to summarize the time to first event in the composite endpoint, by presenting the time-dependent

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cumulative frequency and percentage of patients who reach the primary composite endpoint by treatment group. Appropriate methods for plotting the overall data from both trial parts together will be pre-specified in the statistical analysis plan. Separate Kaplan-Meier plots by trial part will also be provided.

Should one of the three active arms be stopped due to safety reasons or futility, then thereafter the pre-specified testing procedure will be performed for the other arm treating all null hypotheses for the stopped arm as non-rejected. For patients whose treatment is stopped as a result of a data monitoring committee recommendation to suspend treatment in one dose group, follow-up for cardiovascular (CV) and safety events will continue. Since these patients will not receive further study medication, less frequent follow-up will be conducted every 6 months. Continued follow-up would likely enhance understanding of the safety of the other dose groups as well. Follow-up will simply continue in all scenarios until 1,400 patients have had a primary endpoint and the only difference to the pre-planned study conduct will be that the patients in the stopped treatment arms are not being treated after the DMC decision point.

9.4.3 Handling of missing values/censoring/discontinuations

Regarding time-to-event endpoints only observed events will be used in the analysis and in the primary analysis censoring of non-observed events will be assumed to be non-informative. Sensitivity analyses with respect to this assumption will be performed. Incomplete dates of events and censoring dates will be imputed as described below.

In the primary analysis, all patients, including those who discontinue study therapy due to lack of efficacy, adverse events or abnormal laboratory values will be followed until death or the end of the pivotal phase. Information of patients discontinuing study drug or participation in trial visits will be collected whenever possible and will be used in the analysis. In patients who could not be followed up for primary outcome events, it is aimed to at least determine the vital status of the patients at the final pivotal phase visit.

The following rules will be applied separately for the composite MACE endpoint and for all its individual components. Patients who have not experienced the respective endpoint will be censored on the date of the last follow-up in the following way:

- for patients who die, the censoring date will be the date of death unless the patient withdrew his consent for the collection of follow-up information,
- for patients who attend a final visit during pivotal phase close out, the censoring date will be the final visit date,
- otherwise the censoring date will be based on the last pivotal phase visit at which the investigator reported that it was known whether the patient experienced any clinical events since the last visit (i.e. answer of “yes” or “no” to this question, not “unknown”. The last known date the patient was reported alive at that pivotal phase visit will be used, if the last known date the patient was alive is missing the date of the last pivotal phase visit at which it was known whether the patient experienced any clinical events since the last pivotal phase visit will be used.

Should the censoring date lie after the chosen analysis cut-off date, it will be set to the analysis cut-off date.

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If the date of a MACE endpoint or of censoring is not known or is incomplete following all attempts to get an approximate date, a day will be imputed using the following algorithm:

- If only the month of the event is known, then the 15th day of this month will be imputed.
- If only the year of the event is known, then the 1st July will be imputed.
- If year, month and day are unknown, the randomization date will be imputed.
- If this imputation rule leads to a date before the randomization date or after a patient's last pivotal phase visit or after a patient's death, but before the imputation the date could have been on one of these dates, then the date will be imputed as that date.

9.4.4 Supportive analyses

The components of the composite primary efficacy endpoint (CV death, fatal or non-fatal MI, fatal or stroke) will also be analyzed individually in order to evaluate their contributions to the overall treatment effect.

The primary endpoint will also be analyzed on the PPS. Additionally in an on-treatment analysis on the FAS patients will be considered censored at the latest one quarter year + 28 days (119 days) after the last study injection. Besides adjudicated endpoints investigator reported outcomes will also be analyzed.

The three pooled canakinumab doses will be compared to placebo on the primary composite endpoint and its components, because in case of similar efficacy on all three doses this would be the most powerful test of the scientific hypothesis addressed by this trial. Additionally, when all three doses have similar efficacy such a pooled analysis approach may be able to provide the most precise information on the effects in subgroups. Methods to evaluate dose response in terms of cardiovascular events will also be pre-specified in the detailed statistical analysis plan.

Furthermore, pre-specified subgroup analyses will include age, sex, race, ethnicity, BMI, region, glycemic status, smoking status, baseline hsCRP level, LDL-C levels, SBP/DBP levels, statin, aspirin, gout and renal failure. Possible interactions between treatment and baseline variables will be evaluated with appropriate methods. Results will be presented graphically as forest plots. The objective of the subgroup analyses is to show the consistency of treatment effects across a wide variety of patient groups. Additional subgroup analyses will be considered and pre-specified prior to unblinding of trial database for final analysis. Additionally, the post-baseline subgroups of response in hsCRP response and target hsCRP levels achieved will be explored.

A sensitivity analysis will be conducted using randomization plan as an additional covariate or stratification factor in the primary model. A sensitivity with respect to the consistency of treatment effects in the two parts of the trial will also be performed. Finally, in order to achieve approximately 50% of patients < 12 months or ≥ 12 months post index-MI recruitment in one of these subgroups may be stopped earlier than in the other subgroup. If that occurs, then a sensitivity analysis stratifying the primary analysis by time since index MI 30 days to < 6 months, ≥ 6 months to <12 months and ≥ 12 months will be performed.

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9.5 Analysis of key secondary and exploratory variables

Unless otherwise specified all time-to-event analyses will be based on events occurring during the double-blind period of the pivotal phase (see Section 9.4). Dose response in secondary and exploratory variables such as hsCRP will also be explored.

9.5.1 Secondary variables

Key secondary efficacy variables

The following key secondary variables will be used in the analyses:

- Time to the first occurrence of an adjudication committee confirmed composite cardiovascular endpoint consisting of the components of the primary endpoint and hospitalization for unstable angina requiring unplanned revascularization
- Time to adjudication committee confirmed new onset of type 2 diabetes among those with pre-diabetes at randomization

The following hypotheses will be tested with respect to the key secondary variables for the canakinumab 300 mg dose versus placebo

- H_{12}: The hazard rate of first adjudication committee confirmed secondary composite CV endpoint in the canakinumab 300 mg dose group is greater than or equal to the hazard rate of the placebo group
- H_{13}: The hazard rate of new onset of diabetes for pre-diabetic patients in the canakinumab 300 mg dose group is greater than or equal to the hazard rate of the placebo group

Each null hypothesis is tested against the one-sided alternative that the hazard rate is smaller for the canakinumab 300 mg dose group than in the placebo group. The corresponding hypotheses for the comparison of the canakinumab 150 mg dose versus placebo are H_{22} for the secondary composite CV endpoint and H_{23} for the new onset of diabetes endpoint; the corresponding hypotheses for the comparison of the canakinumab 50 mg dose versus placebo are H_{32} for the secondary composite CV endpoint and H_{33} for the new onset of diabetes endpoint.

All key secondary efficacy variables will be analyzed on the FAS with a log-rank test stratified by time since index MI and trial part. The hazard ratios will be estimated using a Cox regression model stratified by time since index MI and trial part. Kaplan-Meier type plots showing each treatment will be provided overall and separately by trial part. The multiplicity adjustment used to protect the familywise type I error rate is shown in Figure 9-1. Based on this testing procedure, once the primary null hypothesis for a dose has been rejected the key secondary endpoints for that dose are tested using a weighted Bonferroni-Holm test (Holm 1979) at the available local significance level for the key secondary endpoints for that dose. The weighting of this Bonferroni-Holm procedure will be 90% for the key secondary CV composite and 10% for the key secondary new onset of diabetes endpoint.

The secondary efficacy variable corresponding to new onset diabetes in patients with prediabetes at randomization will be the time from randomization to the first of repeated FPG ≥126 mg/dL (≥7.0 mmol/L) or the first of repeated HbA1c ≥ 6.5% or start of new anti-diabetic concomitant medication(s) for glucose lowering purpose. Due to the discrete nature

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of the time points when new onset of type 2 diabetes can be determined, events identified at the same pivotal phase visit time point for different patients will be considered as tied events and exact method for handling ties will be used. This assumes that for each of these patients new onset of diabetes occurred at some time point since the previous pivotal phase visit, but that due to the impossibility of continuous monitoring of the patients the true order in which each of them progressed to diabetes is unknown (Allison 1995). For this endpoint, patients without new onset of diabetes will be considered censored at the time of their last laboratory assessment.

Other secondary efficacy variables

Although all-cause mortality is considered a very important secondary endpoint due to its importance as both an efficacy and safety outcome, it is not part of the pre-specified testing procedure for primary and key secondary endpoints, because given the expected number of deaths in the trial it would not have been possible to adequately power the key secondary mortality endpoint.

All-cause death and the composite of all-cause death, stroke or MI will be analyzed on the FAS with a log-rank test stratified by time since index MI and trial part. The hazard ratios will be estimated using a Cox regression model stratified by time since index MI and trial part. Kaplan-Meier plots showing each treatment will be provided overall and by trial part. Patients who did not die will be considered censored at the last time they were reported to be alive.

Analysis of the prediabetes washout period

Data from the double-blind period of the pivotal phase and the prediabetes washout period of the extension phase will be combined to assess to what extent canakinumab truly delayed progression to diabetes and to what extent it only masked diabetes during the pivotal phase double-blind period. The analysis will take into account that masking of diabetes may have occurred in patients not diagnosed as diabetic during the pivotal phase that did not enter the washout period. A number of sensitivity analyses with a range of assumptions about these patients will be performed. These analyses will be specified in a detailed Statistical Analysis Plan.

Analysis of the Post-Stroke Functional Assessment Sub-Study

In line with the primary objective of the post-stroke functional assessment sub-study to evaluate canakinumab arms facilitates functional recovery from stroke, the primary endpoint for this sub-study is the modified Rankin scale assessment 90 days post-stroke. Further endpoints are the 30 day results of the modified Rankin scale assessment, the 30 and 90 day MFSI-SF and the 30 and 90 day SIS-16.

Analyses will be fully specified in a detailed Statistical Analysis Plan and will take into account that while patients were initially randomly assigned to treatments the subset of patients experiencing a stroke may represent a biased subset. The impact of the occurrence of fatal strokes in the main study on the results of the sub-study will also be considered.

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Sub-studies other than the post-stroke functional assessment sub-study have their own protocol specifying the planned analyses. These studies were prematurely terminated and will be reported accordingly.

9.5.2 Exploratory Efficacy variables

Exploratory time-to-event outcomes will be analyzed using Cox models including treatment with time since index MI and trial part as a stratification variable, along with Kaplan-Meier type plots. Exploratory continuous outcome variables (i.e. change from baseline of HbA1c, biomarkers, etc.) will be analyzed using both a repeated measures analysis of covariance adjusted for baseline value, trial part and time since index MI as a factor, as well as a descriptive analysis.

The following endpoints will be analyzed

- Time to other cardiovascular disorders with a known inflammatory component:
    - Time to first deep vein thrombosis/pulmonary embolism
    - Time to first supraventricular tachycardia/atrial fibrillation
    - Time to first stent thrombosis (probable or definite)
    - Time to first hospitalization or prolongation of hospitalization for heart failure
    - Time to first event of major coronary events composite (CHD death or MI)
    - Time to first event of total vascular events composite consisting of primary endpoint, hospitalization for unstable angina, or for any other non-coronary ischemic event (transient ischemic attack or limb ischemia), any revascularization procedure (coronary and non-coronary), coronary angiography and limb amputation
    - Time to first event of coronary revascularization procedures (PCI or CABG)
    - Time to first event of stroke by etiology
- It will be explored whether the early high induction dose regimen in 300 mg canakinumab arm has an impact on early (within 90 days of randomization) primary and secondary clinical cardiovascular events when compared to the placebo arm and to the 150 mg or 50 mg canakinumab arm with no early high, induction dose regimen.
- Time to nephropathy as assessed by urine albumin/creatinine ratio (≥ 30 mg/mmol) in patients with T2DM or pre-diabetes at baseline
- Glycemic control among those with type 2 diabetes at baseline defined by HbA1c and/or FPG or medical history and/or concomitant medications criteria in Section 4 (analyses will use baseline HbA1c, and baseline BMI as continuous covariates and the use of diabetic medications at baseline (yes/no) as a factor in the analysis models).
    - Time to failure of glycemic control defined as HbA1c ≥ 7.5% confirmed by a second HbA1c within 6 weeks in those patients that were diabetic at baseline with a baseline HbA1c < 7.0%
    - Change from baseline in HbA1c overall and by visit in all patients that were diabetic at baseline

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- Study drug washout in prediabetic patients: to assess the durability of any potential antidiabetic effect of canakinumab in prediabetic patients following washout of study drug as defined in Section 9.5.1 under "Analysis of the prediabetes washout period"
- Change from baseline in biomarkers of cardiovascular and diabetes risk, including but not limited to inflammatory biomarkers, glycemic control markers, β-cell function markers, FPG, and HbA1c including:
  - Achieved reductions from baseline in hsCRP
  - Target hsCRP levels achieved
- In patients with age-related macular degeneration at baseline occurrence of worsening and/or need for treatment and in patients without age-related macular degeneration occurrence thereof and/or need for treatment will be summarized and analyzed using time-to-event methods including ones taking into account predictive covariates.

9.5.3 Safety variables

Safety will be evaluated based on the safety set (SAF). The assessment of safety will be based primarily on the assessment of potential and identified risks defined in the safety profiling plan (SPP), the frequency of adverse events, laboratory abnormalities, and serious adverse events suspected by the investigators to be related to study treatments. Other safety data (like vital signs, ECG) will be summarized as appropriate.

As appropriate overall (i.e. across the two trial parts) absolute risk differences, risk ratios, hazard ratios or odds ratios for each active dose versus placebo will be calculated taking into account the trial part to avoid any confounding of the safety assessment through differential follow-up or differences in patient populations.

Adverse events between informed consent and randomization

Adverse events between informed consent and randomization will be summarized by primary system organ class and preferred term. This summary will include events that would qualify as trial endpoints if they occurred after randomization, but which are to be reported as AEs prior to randomization.

Adverse events (AEs) excluding trial endpoints

The incidence of treatment emergent AEs (events started on the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) excluding trial endpoints for the pivotal phase will be summarized by primary system organ class (SOC), preferred term and also by severity and relationship to study treatment. Standardized MedDRA Queries (SMQs) may also be employed. The MedDRA version used for reporting the study will be clearly identified.

If a patient reported more than one AE with the same preferred term, the AE with the greatest severity will be presented. If a patient reported more than one AE within the same primary system organ class, the patient will be counted only once with the greatest severity at the system organ class level, where applicable.

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The number and percentage of patients reporting any AE during the double-blind period of the pivotal phase will be summarized by primary system organ class, preferred term and treatment, and also by SMQ and treatment if needed.

Separate summaries will be provided for study drug related AEs, deaths, SAEs and, other significant AEs leading to discontinuation.

Similar summaries will be provided for the extension phase.

AEs of special interest

Frequencies of adjudicated immunological AEs (serious allergies/immunological events (e.g. immunological laboratory screen and anti-canakinumab antibodies), serious infections, and malignancies, whether newly detected or worsening of existing malignancies) will be reported. For the extension phase no adjudication of AEs will be performed.

Laboratory data

The summary of laboratory evaluations will be presented for three groups of laboratory tests (Hematology, Serum chemistry and Urinalysis).

Descriptive summary statistics for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by laboratory test and treatment group. Change from baseline will only be summarized for patients with both baseline and post baseline values.

In addition, shift tables by treatment group will be provided for all parameters (except for creatinine clearance, which will be calculated using the MDRD formula) in order to compare a patient's baseline laboratory evaluation relative to all post-baseline values.

The frequency and percentage of patients with clinically notable laboratory results after baseline will be tabulated.

Liver safety

The following analyses will be performed for the pivotal phase:

- The liver-related events meeting specified criteria standard table will be used to provide the number and percentage of patients having aspartate transaminase (AST), alanine transaminase (ALT) > 3, 5, 8, 10 x ULN or total bilirubin (TBL) >1.5, 2 x ULN or alkaline phosphatase (AP) > 2, 3 x ULN. The number and percentage of potential Hy's Law cases will be presented by treatment group. Potential Hy's Law cases are defined as those patients with AST or ALT >3xULN and TBL >2xULN and AP <2xULN at the same lab measurement.
- A cross-tabulation of baseline and worst post-baseline values by below, within and above normal range categories will be provided. Shift tables will be provided for the parameters AST, ALT, TBL and AP. These summaries will be presented by laboratory test and treatment group.
- Standard laboratory tables will be produced as for all other laboratory parameters.

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- The narrow and broad "Possible drug related hepatic disorders – comprehensive search" SMQ and the corresponding lower level SMQs will be presented including the respective preferred term frequencies covered under the SMQs.
- The overall SMQ/preferred term table will be used to provide the number and percentage of patients with hepatic disorders.
- eDISH (electronic Drug-Induced Serious Hepatotoxicity) plots will be provided representing the entire study population.
- Narratives for any patients discontinued due to liver function abnormalities will be prepared.

Vital signs

Descriptive summary statistics of vital sign variables for the change from baseline to each post baseline visit will be presented. These descriptive summaries will be presented by vital sign and treatment group. Change from baseline will only be summarized for patients with both baseline and post-baseline values.

ECG

Based on a standard 12-lead ECG, any new or worsening clinically relevant findings will be recorded as AEs except for ECG changes constituting study endpoints. Therefore, no separate presentation of ECG findings is foreseen.

9.5.4 Resource utilization

Analyses of healthcare resource utilization data will be specified separately.

9.5.5 Patient Reported Outcomes

Exploratory efficacy patient reported outcome variables including those related to tiredness, physical function, performance function and health status, will be generated from the Modified Rankin Scale, MGSI-SF, SF-36, SIS-16, EQ-5D Health State Classification and Visual Analogue Scale. These will be analyzed using a repeated measures analysis of covariance with baseline levels as a covariate and summarized descriptively.

EQ-5D

Health state classification will be converted to a score (during data analysis stage) according to a list provided. This list has 243 values for all possible EuroQoL health status. For example, a health state of 11111 will have a score of 1.00 and a health status of 12132 will have a score of 0.09.

The analysis will involve the estimation of weighted indices over time for patients in each treatment group. The weighted indices will be displayed graphically along with the respective treatment means. The change from baseline in VAS scores will also be summarized using descriptive statistics.

Analysis based on EQ-5D data will be reported separately, and will not be part of the clinical study report. This will also apply to the extension phase.

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9.5.6 Pharmacokinetics

A mixed effects modeling approach may be used to characterize the PK of canakinumab and it's binding to IL-1β. The relationship between population parameters such as CL/F and covariates such as dose, age, and weight may be investigated using graphical methods and simple regression models. Quality of individual fits to the dataset will be assessed, and individual model parameters (post-hoc estimates) may be obtained for each patient. Alternatively, in case the population based modeling may not be feasible, the analysis will be limited to the methodology based on predictive check, where the measures of systemic drug exposure (pre-dose trough levels) and biomarker response (IL-1 β) will be plotted against the data collected in previous trials.

No pharmacokinetic data will be generated during the extension phase.

9.5.7 Pharmacogenetics/pharmacogenomics

Pharmacogenetics

The exploratory pharmacogenetic studies are designed to investigate the association between genetic factors (genotypes) and clinical assessments (phenotypes) which are collected during the pivotal phase of the clinical trial. Without prior evidence of a strong association, a number of possible associations are evaluated with exploratory analyses. A range of statistical tests (chi-square tests, ANCOVAs, linear and logistic regression) are used for the analyses. Additional data, from subsequent clinical trials, are often needed to confirm associations. Alternatively, if the numbers of patients enrolled in the study are too small to complete proper statistical analyses, these data may be combined, as appropriate, with those from other studies to enlarge the data set for analysis.

No pharmacogenetic data will be generated during the extension phase.

Pharmacogenomics

For pharmacogenomics, messenger RNA (mRNA) will be extracted from blood samples. mRNA will be analyzed for gene expression using gene expression microarrays such as Affymetrix microarray technology and/or quantitative RT-PCR. Quality control of all individual RNA samples and expression data will be conducted. The gene expression data will be analyzed using several different algorithms including various clustering analysis algorithms, ANOVA correlation analysis, and different filtering strategies based on magnitude and statistical significance of differences of gene expression.

No pharmacogenomic data will be generated during the extension phase.

9.5.8 Biomarkers

Biomarkers associated with cardiovascular disease will be measured. These may include but are not limited to IL-1ra, IL-6, IL-18, leptin, adiponectin, TNFα, PAI-1 and fibrinogen

Descriptive statistics will be provided by treatment group for the FAS including geometric mean and 95% confidence intervals for the geometric mean.

No biomarkers will be measured during the extension phase.

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9.5.9 PK/PD

Refer to Section 9.5.6

9.6 Sample size calculation

Expected event rates in a secondary prevention trial in patients with prior MI

In spite of differences in eligibility criteria and outcome definitions, several recent trials provide useful information on the expected rates of the endpoint in the proposed trial, and support the focus on hard endpoints. The ARISE trial (Tardif et al. 2008) randomized 6,144 patients with recent acute coronary syndrome (between 14 and 365 days before enrollment) to succinobucol vs. placebo and followed them for an average of 2 years. The observed incidence on the composite endpoint of cardiovascular death, MI, stroke or cardiac arrest corresponds to an incidence rate of 5.1 events per 100 person-years.

The PROVE-IT TIMI-22 trial (Cannon et al. 2004) provides an additional estimate of event rates in post-acute coronary syndrome patients (71% post MI), randomized within less than 10 days post index event. Over an average follow-up of 2 years, the 2,099 patients in that trial randomized to receive 80 mg of atorvastatin daily had a cumulative incidence of myocardial infarction or death from coronary heart disease of 7.2%. This corresponds to an incidence rate of 3.7 events per 100 person-years. The addition of stroke and other cardiovascular deaths to this endpoint might be expected to increase this rate to over 4 events per 100 person-years.

The WIZARD trial (O'Connor et al. 2003) provides an additional estimate of event rates based on somewhat different eligibility criteria. That trial randomized individuals with a history of myocardial infarction anytime in the past who also had a C pneumoniae IgG titer of 1:16 or more to azithromycin or placebo and followed these people for an average of 14 months. In 7,722 patients followed for the endpoint of recurrent myocardial infarction or death a total of 600 experienced the event with a median follow up of 14 months, corresponding to an incidence rate of 6.7 events per 100 person-years.

Levels of hsCRP in patients with prior myocardial infarction are powerful predictors of subsequent events. Rates of recurrent events are 30% to 60% higher in patients with hsCRP≥2 mg/L relative to lower levels, regardless of the intensity of statin treatment (Ridker et al. 1998). While aggressive lipid-lowering with statins reduces levels of hsCRP, elevations remain common in post-MI patients. Specifically, in the PROVE-IT TIMI-22 trial, 43% of patients randomized to 80 mg atorvastatin daily had on-treatment levels of hsCRP ≥ 2 mg/L (Ridker et al. 2005). A similar prevalence of elevated hsCRP was observed in patients treated with 80 mg simvastatin daily in the Aggrastat-to-Zocor trial (Morrow et al. 2006). In the primary prevention setting of the JUPITER trial (Ridker et al. 2008), 20 mg of rosuvastatin substantially reduced levels of hsCRP from a baseline median of 3.2 mg/L, but on-treatment median levels in the active treatment group remained above 2 mg/L at all follow-up visits.

The event rates from these trials that have included individuals with prior myocardial infarction, with the additional consideration of the increased MACE rate associated with an elevated level of hsCRP, appear to support an estimate of the expected MACE rate of 3.25 to 4 per 100 person-years in the placebo group. This range already takes into consideration that full-dose statin therapy will most likely be used by such patients. The expected risk during the

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first year of the trial is expected to be higher for patients randomized within 30 days to 6 months of their index MI, than for patients randomized longer after their index MI.

The observed blinded event rate at the time of protocol amendment 8 appears to be at the upper end of the previously expected range despite a lower than expected enrollment into the <6 month and <12 month post-index MI subgroups. The blinded event rate also appears to be stable over time into the second year of follow-up based on the current follow-up information (on average less than a year and up to 2.5 years in the first patients enrolled).

Needed number of patients with primary endpoints and Sample size

As shown in Table 9-1 1,400 patients across all three trial arms with an observed major cardiovascular disease event (MACE) provide ≥ 90% power for demonstrating the superiority of at least one dose of canakinumab over placebo using the closed testing described in Section 9.4 Analysis of the primary variable (s) at the one-sided 2.45% level available for the final analysis if all doses have a true 20% net relative hazard reduction compared to placebo for MACEs after discounting for discontinuations of treatment. Additionally, in this case both the 150 mg dose and 50 mg dose have ≥ 80% power to become significant.

Table 9-1 Power at the final analysis for 1,400 patients with a MACE

True relative risk reduction			Power [%]				
300 mg [%]	150 mg [%]	50 mg [%]	**at least one dose significant**	300 mg	150 mg	50 mg	all doses significant
25.0	25.0	25.0	**99.4**	93.5	96.1	96.3	89.0
22.5	22.5	22.5	**97.9**	85.4	90.4	91.4	76.5
20.0	20.0	20.0	**93.6**	72.0	80.6	80.3	56.9
17.5	17.5	17.5	**83.7**	54.9	65.8	63.9	35.8
22.5	22.5	0	**94.9**	82.3	88.1	1.9	1.9
20.0	20.0	0	**87.5**	67.6	77.2	1.8	1.8
22.5	17.5	10.0	**89.0**	81.6	64.9	24.7	20.9

Power results are based on 5,000 simulated trials per scenario. Only results for primary endpoints were simulated, therefore the actual power will be slightly higher as significant key secondary endpoints for one dose may make more alpha available for the primary endpoint of the other dose. All simulations were performed in SAS 9.2 (TS1M0) on an AIX 6.1 platform.

Depending on the exact distribution of endpoints across the three trial arms either the 150 mg dose would need to achieve a relative risk reduction of 15 to 16% versus placebo, or the 300 or 50 mg dose would need to achieve a relative risk reduction of 17 to 18% versus placebo in order for any dose to become significant. Once that is the case relative risk reductions of approximately 14 to 16% may become significant for the other doses.

A sample size of approximately 10,000 randomized patients is expected to be sufficient to accrue the planned number of 1,400 patients with a MACE in approximately 6 years. Given a 20% relative risk reduction in all active treatment arms, reducing the sample size from 17,200 patients to approximately 10,000 randomized patients reduces the expected number of patients with events in the 50 mg dose by less than 4% (11 patients with an event). Thus, the impact of the reduction in sample size on the power for the 50 mg dose will be negligible.

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In order to achieve the planned number of events and preserve the target power of the study the event rate of the primary endpoint will be monitored in a blinded fashion so that adjustments can be made to the number of patients to be randomized and/or the duration of follow-up.

No sample size calculation was performed for the extension phase, because the objective of the extension phase is long-term safety assessment in participants of the pivotal phase.

9.7 Power for analysis of key secondary variables

The revised sample size following amendment 6 was determined solely based on the primary endpoint, the initial calculations for the power of the key secondary variables were therefore not updated.

9.8 Interim analyses

Interim analyses of efficacy, futility and safety will be carried out during the pivotal phase of the study. Two interim analyses of efficacy will be performed when about 50% of the target number of primary cardiovascular events have been accumulated and the second one when 75% of the planned number of events are available. Criteria for the interim and final analyses will be determined using a fixed Bonferroni split of the alpha allocated to the interim analyses and to the final analyses in order to protect the overall one-sided familywise type I error rate across all analyses at 2.5%. The fixed total one-sided alpha allocated to both interim analyses of efficacy combined is 0.05%. Of this 0.01% is allocated to the first efficacy interim analysis and 0.04% allocated to the second efficacy interim analysis. The one-sided significance level for the final analysis is thus 2.45%.

Interim analyses for futility will be conducted simultaneously with the two analyses of efficacy. One additional futility analysis may also be performed earlier than first planned efficacy IA (at approximately 50% primary events), but only after a sufficient number of primary events are accrued, i.e., >25%. It should be noted that the efficacy criteria are not modified to “buy back” alpha based upon the presence of futility boundaries; this conservative approach ensures that the familywise type I error rate of the study is protected.

Full details on boundaries and stopping rules will be pre-specified in the Charter of the Data Monitoring Committee (DMC). Timing and number of safety analyses will also be specified in DMC charter.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

This will also apply for the extension phase.

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10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

This study includes an optional pharmacogenetic/pharmacogenomics component which requires a separate signature if the patient agrees to participate. It is required as part of this protocol that the Investigator presents this option to the patient. The process for obtaining informed consent should be exactly the same as described above for the main informed consent.

Declining to participate in this pharmacogenetic/ pharmacogenomics assessment will in no way affect the patient's ability to participate in the main research study.

In the event that Novartis wants to perform testing on the samples that are not described in this protocol, additional Institutional Review Board and/or ethics committee approval will be obtained.

The informed consent form will be updated to include details of the extension phase. Patients may only be included in the main drug dispensing period of the extension phase (Visit 201 and beyond) after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent as described above.

10.3 Responsibilities of the investigator and IRB/IEC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs, and regulatory authorities as

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required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

The above will also apply for the extension phase. The extension phase will be introduced via a protocol amendment. The informed consent form will be amended accordingly.

10.4 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be submitted for publication and posted in a publicly accessible database of clinical study results regardless of study outcome.

10.5 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed by Novartis Pharma Auditing and Compliance Quality Assurance, a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal Standard Operating Procedures (SOPs), and are performed according to written Novartis processes.

This will also apply for the extension phase.

11 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations during the pivotal and extension phases. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the trial to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC. Only amendments that are required for patient safety may be implemented prior to IRB/IEC approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such

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cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed within 10 working days.

This will also apply for the extension phase.

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13 Appendix 1: Clinically notable laboratory values and vital signs

Laboratory notable range deviations will be provided in the investigator binder.

Vital sign notable range deviations

VITAL SIGNS		NOTABLE ABNORMALITIES
Pulse (beats/min)		either ≥120 + increase ≥25* or >130
		either ≤50 + decrease ≥30* or < 40
Blood pressure (mmHg)	systolic	either ≥180 + increase ≥30* or > 200
		either ≤90 + decrease ≥30* or < 75
	diastolic	either ≥105 + increase ≥20* or > 115
		either ≤50 + decrease ≥20* or < 40
Weight		a weight change of > 10% during the study

*Refers to post-baseline value as compared to baseline value

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14 Appendix 2 PK / PD/ IG Blood Collection Log

Table 14-1 PK / PD Blood Collection Log

Visit	Month	PK(pre-dose)			PD		IG	
		Canakinumab			IL-1β			
		PK Collection #	Sample #	mL	Sample #	mL	Sample #	mL
2	Baseline	1	1	2	101	3	201	2
7	Month 12	2	2	2	102	3	202	2
11	Month 24	3	3	2	103	3	203	2
EOS		4	4	2	104	3	204	2
Unscheduled Visit			1001, 1002, 1003,	2	1101, 1102, 1103,	3	1201, 1202, 1203	2

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15 Appendix 3 Study Endpoint Definitions

15.1 Definition of Cardiovascular Death

Cardiovascular death includes sudden cardiac death, death due to acute myocardial infarction, death due to heart failure, death due to stroke, and death due to other cardiovascular causes.

Sudden cardiac death: A sudden death that occurs in a previously stable patient who does not have a prior terminal condition, such as malignancy not in remission or end-stage chronic lung disease.

Established sudden cardiac death includes the following deaths:

Witnessed and instantaneous without new or worsening symptoms.

Witnessed within 60 minutes of new or worsening symptoms.

Witnessed and attributed to an identified arrhythmia (e.g., captured on ECG recording or witnessed on a monitor by either a medic or paramedic or unwitnessed but found on implantable cardioverter-defibrillator review).

After unsuccessful resuscitation from cardiac arrest

After successfully resuscitated from cardiac arrest and without identification of a non-cardiac etiology (Post-Cardiac arrest Syndrome)

Unwitnessed death without other cause of death

General Considerations

A patient seen alive and clinically stable 12-24 hours prior to being found dead without any evidence or information of a specific cause of death should be classified as an "Unwitnessed Death." Typical scenarios include

• Patient well the previous day but found dead in bed the next day

• Patient found dead at home on the couch with the television on

Deaths for which there is no information beyond "Patient found dead at home" may be classified as "Undetermined Cause of Death"

Death due to Acute Myocardial Infarction (AMI): refers to a death within 30 days after a myocardial infarction (MI) related to consequences seen immediately after the myocardial infarction, such as progressive congestive heart failure (CHF), inadequate cardiac output, or recalcitrant arrhythmia. If these events occur after a "break" (e.g., a CHF and arrhythmia free period), they should be designated by the immediate cause. The acute myocardial infarction should be verified either by the diagnostic criteria outlined for acute myocardial infarction or by autopsy findings showing recent myocardial infarction or recent coronary thrombus, and there should be no conclusive evidence of another cause of death.

Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood should be considered death due to acute myocardial infarction.

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If death occurs before biochemical confirmation of myocardial necrosis can be obtained, adjudication should be based on clinical presentation and ECG evidence.

Death resulting from a procedure to treat myocardial ischemia or to treat a complication resulting from myocardial infarction should also be considered death due to acute MI.

Death due to a myocardial infarction that occurs as a direct consequence of a cardiovascular investigation/procedure/operation should be classified as death due to other cardiovascular cause.

Death due to Heart Failure or Cardiogenic Shock: refers to death occurring in the context of clinically worsening symptoms and/or signs of heart without evidence of another cause of death.

Death due to Heart Failure or Cardiogenic shock should include sudden death occurring during an admission for worsening heart failure as well as death from progressive heart failure or cardiogenic shock following implantation of a mechanical assist device.

New or worsening signs and/or symptoms of congestive heart failure (CHF) include any of the following:

- New or increasing symptoms and/or signs of heart failure requiring the initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving maximal therapy for heart failure
- Heart failure symptoms or signs requiring continuous intravenous therapy or chronic oxygen administration for hypoxia due to pulmonary edema
- Confinement to bed predominantly due to heart failure symptoms
- Pulmonary edema sufficient to cause tachypnea and distress not occurring in the context of an acute myocardial infarction, worsening renal function, or as the consequence of an arrhythmia occurring in the absence of worsening heart failure
- Cardiogenic shock not occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure.

Cardiogenic shock is defined as systolic blood pressure (SBP) < 90 mm Hg for greater than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion:

- Cool, clammy skin *or*
- Oliguria (urine output < 30 mL/hour) *or*
- Altered sensorium *or*
- Cardiac index < 2.2 L/min/m2

Cardiogenic shock can also be defined if SBP < 90 mm Hg and increases to ≥ 90 mm Hg in less than 1 hour with positive inotropic or vasopressor agents alone and/or with mechanical support.

Death due to Stroke (intracranial hemorrhage or non-hemorrhagic stroke): refers to death occurring up to 30 days after a suspected stroke based on clinical signs and symptoms as well as neuroimaging and/or autopsy, and where there is no conclusive evidence of another cause of death.

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Death due to Other Cardiovascular Causes: refers to death due to a cardiovascular cause not included in the above categories (e.g. dysrhythmia, pulmonary embolism, cardiovascular intervention, aortic aneurysm rupture, or peripheral arterial disease). Mortal complications of cardiac surgery or non-surgical revascularization, even if "non-cardiovascular" in nature, should be classified as cardiovascular deaths.

Death of Undetermined Cause (presumed cardiovascular) :

All deaths not attributed to the categories of Cardiovascular Death or to a Non-cardiovascular cause are considered presumed cardiovascular deaths.

15.2 Non-cardiovascular death

Non-Cardiovascular death is defined as any death not covered by cardiac death or vascular death and is categorized as follows:

Pulmonary causes
Renal causes
Gastrointestinal causes
Infection (including sepsis)
Non-infectious causes
Malignancy
Accident/Trauma
Suicide
Non-cardiovascular system organ failure (e.g. Hepatic)
Hemorrhage, not intracranial
Other. Please specify.

15.3 Definition of Non-fatal Myocardial Infarction

Acute Myocardial Infarction: the term myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for MI.

Spontaneous MI : Detection of rise and/or fall of cardiac biomarkers with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:

- Symptoms of ischemia
- ECG changes indicative of new ischemia (new ST-T changes or new LBBB)*
- Development of pathological Q waves in the ECG**
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- *ECG manifestation of acute myocardial ischemia (in the absence of LVH and LBBB):
- ST Elevation - New ST elevation at the J-point in two contiguous leads with the cut-off points:
- $\geq$ 0.2 mV in men or $\geq$ 0.15 mV in women in leads V2-V3 and/or $\geq$ 0.1 mV in other leads.

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- ST depression and T-wave changes – New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or T inversion ≥ 0.1 mV in two contiguous leads with prominent R waves or R/S ratio >1.
- **Pathological Q waves:
  1. Any Q-wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3
  2. Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 an any two leads of a contiguous lead grouping (I, aVL, V6, V4-V6, II, III, aVF).

Percutaneous Coronary Intervention (PCI) related Myocardial Infarct ; For PCI in patients with normal baseline troponin values elevations of cardiac biomarkers above the 99th percentile URL within 24 hours of the procedure are indicative of peri-procedural myocardial necrosis. By convention increases of biomarkers greater than 3 x 99th percentile URL are consistent with PCI related myocardial infarction.

- If the cardiac biomarker is elevated prior to PCI a ≥ 20% increase of the value in that second cardiac biomarker within 24 hours of the PCI and documentation that cardiac biomarkers were decreasing (two samples at least 6 hours apart) prior to the suspected recurrent MI is also consistent with PCI related MI.
- Symptoms of cardiac ischemia are not required
- CABG related Myocardial Infarct : For CABG in patients with normal baseline troponin, elevations of cardiac biomarkers above 5 times the 99th percentile of the normal reference range during the first 72 hours after CABG, when associated with

EITHER

New pathological Q waves in at least 2 contiguous leads on the ECG that persist through 30days or new LBBB

OR

Angiographically documented new graft or native coronary artery occlusion

OR

Imaging evidence of new loss of viable myocardium

Is consistent with CABG related Myocardial Infarct.

- If the cardiac biomarker is elevated prior to CABG a ≥ 20% increase of the value in the second cardiac biomarker within 72 hours of CABG AND documentation that the cardiac biomarkers were decreasing (2 samples at least 6 hours apart) prior to the suspected recurrent MI plus either new pathological Q waves in at least 2 contiguous leads on the ECG or new LBBB, angiographically documented new graft or native artery occlusion or imaging evidence or new loss of viable myocardium is consistent with a peri-procedural myocardial infarct after CABG.
- Symptoms of cardiac ischemia are not required.

Criteria for Prior Myocardial Infarction : Any of the following criteria meets the diagnosis for prior myocardial infarction:

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- Development of new pathological Q waves with or without symptoms
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract in the absence of a non-ischemic cause
- Pathological findings of a healed or healing myocardial infarction

ECG changes associated with prior Myocardial Infarction:

- Any Q wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3
- Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6, V4-V6, II, III, and aVF)
- R-wave ≥ 0.04 seconds in V1-V2 and R/S ≥ 1 with a concordant positive T-wave in the absence of a conduction defect

Criterion for Reinfarction: In patients where recurrent MI is suspected from clinical signs or symptoms following the initial infarction, an immediate measurement of the employed cardiac biomarker is recommended. A second sample should be obtained 3-6 hours later. Recurrent infarction is diagnosed if there is a ≥ 20% increase of the value in the second sample. This value should exceed the 99th percentile URL. However if cardiac biomarkers are elevated prior to the suspected new MI, there must also be documentation of decreasing values (two samples at least 6 hours apart) prior to the suspected new MI. If the values are falling criteria for reinfarction by further measurement of biomarkers together with features of the ECG or imaging can be applied.

ECG diagnosis of reinfarction following the initial infarction : may be confounded by the initial evolutionary ECG changes. Reinfarction should be considered when the ST elevation ≥ 0.1 mV reoccurs in an inpatient having a lesser degree of ST elevation or new pathognomonic Q-waves, in at least two contiguous leads, particularly when associated with ischemic symptoms for 10 minutes or longer, The re-evaluation of the ST segment can, however also be seen in threatening myocardial rupture and should lead to additional diagnostic work-up. ST depression or LBBB on their own should not be considered valid criteria for Myocardial Infarction.

If biomarkers are increasing or peak is not reached then there is insufficient data to diagnose recurrent MI.

Clinical Classification of different types of Myocardial Infarction :For each MI identified a Type of MI will be assigned using the following guidelines:

- Type 1 – Spontaneous MI related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring or dissection.
- Type 2 – MI secondary to ischemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, anemia, hypotension, coronary embolism, arrhythmias, hypertension or hypotension.
- Type 3 –Sudden unexpected cardiac death including cardiac arrest, often with symptoms suggestive of myocardial ischemia accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained or at a time before the appearance of cardiac biomarkers in the blood.

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- Type 4a –MI associated with PCI.
- Type 4b –MI associated with stent thrombosis as documented by autopsy or angiography.
- Type 5 –MI associated with CABG.

Silent MI

The following criteria will be used by the central ECG reading vendor to define interval "silent" (no clinical symptoms or signs) MI between baseline and yearly ECGs:

Criteria for MI (Surawcz, Ed : Chou's Electrocardiography in Clinical Practice, 5th Edition, 2001).

Myocardial infarctions are reported only on the basis of pathologic Q waves. Pathologic Q waves are defined as Q wave duration > 40ms **and** Q/R ratio = 1/3.

Any Q wave in V1 or V2 that is followed by an R wave should be considered abnormal.

When pathologic Q waves (i.e., myocardial infarction) are present, ST elevation or T wave inversion may be used to classify the infraction as New or Acute. However, ST elevation or T wave inversion in the absence of pathologic Q waves are not sufficient criteria for diagnosis of myocardial infarction.

- **Anterolateral MI** - Pathologic Q waves in leads V3-V6.
- **Anterior MI** - Pathologic Q waves in V3 and V4.
- **Anteroseptal MI** - Pathologic Q waves or QS in leads V1-V4.
- **Extensive Anterior MI** - Pathologic Q waves in leads I, aVL, and V1-V6.
- **High lateral MI** - Pathologic Q waves in leads I and aVL.
- **Inferior MI** - Pathologic Q waves or QS in at least two of the inferior leads: aVF, III, II.
- **Lateral MI** - Pathologic Q waves in leads I, aVL, and V5-V6.
- **Septal MI** - Pathologic Q waves or QS in leads V1-V2, (V3). **In the presence of LAHB or LVH a Q or QS in V3 is required.**
- **Posterior MI** - Initial R wave duration 40 ms in V1 or V2, and R > S and upright T wave; Inferior or Lateral MI are usually also present.

New MI

These criteria for MI are more stringent than the Expert Consensus Document criteria, requiring Q waves to be $\geq$ 0.04 sec in duration and an R/S ratio $\geq$ 1/3. These criteria (drawn from the cardiology literature) are designed to minimize the false positive detection of MIs due to very small physiologic Q waves in the inferior and anterolateral leads.

15.4 Definition of Stroke

Stroke: is defined as the rapid onset of a new persistent neurological deficit attributed to an obstruction in cerebral blood flow and/or cerebral hemorrhage with no apparent non-vascular cause (e.g. tumor, trauma, infection). Available neuroimaging studies will be considered to support the clinical impression and to determine if there is a demonstrable lesion compatible

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with an acute stroke. Non-fatal strokes will be classified as ischemic, hemorrhagic or unknown.

For the diagnosis of Stroke, the following 4 criteria should be fulfilled:

1. Rapid onset* of a focal/global neurological deficit with at least one of the following:
   Change in level of consciousness
   Hemiplegia
   Hemiparesis
   Numbness or sensory loss affecting one side of the body
   Dysphasia/aphasia
   Hemianopsia
   Amaurosis Fugax
   Other new neurological sign/symptom(s) consistent with stroke
   *if the mode of onset is uncertain, a diagnosis of stroke may be made provided that there are no plausible non-stroke causes for the clinical presentation.
2. Duration of a focal/global neurological deficit:
   ≥ 24 hours
   OR
   < 24 hours if:
   This is because of at least one of the following interventions

Pharmacologic (i.e. Thrombolytic drug administration)

Non-pharmacologic (i.e. Neurointerventional procedure (e.g. Intracranial angioplasty)

OR

3. Available brain imaging clearly documents a new hemorrhage infarct
   OR
4. The neurological deficit results in death.

No other readily identifiable non-stroke cause for the clinical presentation (e.g. Brain tumor, trauma, infection, hypoglycemia, peripheral lesion)

Confirmation of the diagnosis by at least on of the following:

Neurology or neurosurgical specialist

Brain imaging procedure (at least one of the following):

i. CT scan

ii. MRI scan

iii. Cerebral vessel angiography

Lumbar puncture (i.e. Spinal fluid analysis diagnostic of intracranial hemorrhage)

If the acute focal signs represent a worsening of a previous deficit, these signs must have either:

- Persisted for more than one week or
- Persisted for more than 24 hours and were accompanied by an appropriate new MRI or CT scan finding

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Strokes are sub-classified as follows:

Ischemic (non-hemorrhagic): A stroke caused by an arterial occlusion due to either a thrombotic) e.g. Large vessel disease/atherosclerotic or small vessel/lacunar) or embolic etiology

Hemorrhagic: A stroke due to a hemorrhage in the brain as documented by neuroimaging or autopsy. This category will include strokes due to primary intracerebral hemorrhage (intraparenchymal or intraventricular), ischemic strokes with hemorrhagic transformation (i.e.; no evidence or hemorrhage on an initial imaging study but appearance on a subsequent scan), subdural hematoma*, and primary subarachnoid hemorrhage.

*All subdural hematomas that develop during the clinical trial : should be recorded and classified as either traumatic versus non traumatic.

Unknown: the stroke type could not be determined by imaging or other means (e.g. Lumbar puncture, neurosurgery, or autopsy) or no imaging was performed

Stroke Disability

Stroke disability can be classified using an adaptation of the modified Rankin Scale as follows:

0: No symptoms at all

1: No significant disability despite symptoms; able to carry out all usual duties and activities

2: Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance

3: Moderate disability; requiring some help, but able to walk without assistance

4: Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance

5: Severe disability; bedridden, incontinent and requiring constant nursing care and attention

6: Dead

15.5 Definition of Stent Thrombosis

1. Stent Thrombosis: Timing:

Type	Timing
Acute stent thrombosis*	0 to 24 hours after stent implantation
Subacute stent thrombosis	> 24 hours to 30 days after stent implantation
Late stent thrombosis†	> 30 days to 1 year after stent implantation
Very late stent thrombosis†	> 1 year after stent implantation
Stent thrombosis should be reported as a cumulative value over time and at the various individual time points specified above. Time 0 is defined as the time point after the guiding catheter has been removed and the patient has left the catheterization laboratory. ***Acute or subacute can also be replaced by the term early stent thrombosis. Early stent thrombosis (0 to 30 days) will be used in the remainder of this document.** **†Includes primary as well as secondary late stent thrombosis; secondary late stent thrombosis is a stent thrombosis after a target lesion revascularization.**	

2. ARC Definitions of Definite, *Probable and Possible Stent Thrombosis

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Definite Stent Thrombosis

Definite stent thrombosis is considered to have occurred by either angiographic or pathological confirmation:

a. Angiographic confirmation of stent thrombosis: The presence of a thrombus that originates in the stent or in the segment 5mm proximal or distal to the stent and presence of at least 1 of the following within a 48 hour time window:
   1. Acute onset of ischemic symptoms at rest
   2. New ischemic ECG changes that suggest acute ischemia
   3. Typical rise and fall in cardiac biomarkers
   4. Non-occlusive thrombus :
      a. Intracoronary thrombus is defined as a (spherical, ovoid or irregular) non calcified filling defector lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections or persistence or contrast material within the lumen, or a visible embolization or intraluminal material downstream.
   5. Occlusive thrombus
      a. TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch)
      b. Pathological confirmation of stent thrombosis. Evidence of recent thrombosis within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy.

Probable Stent Thrombosis

Clinical definition of probable stent stenosis is considered to have occurred after intracoronary stenting in the following cases:

a. Any unexplained death within the first 30 days
b. Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other cause.

15.6 Definition of Unstable Angina Requiring Unplanned Revascularization

Unstable Angina requiring Unplanned Revascularization is defined as :

No elevation in cardiac biomarkers

and

Clinical presentation (one of the following) with cardiac symptoms lasting ≥10 minutes and considered to be myocardial ischemia on final diagnosis

Rest angina or

New onset (<2 months) severe angina (CCS* classification severity ≥ III) or

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Increasing angina (in intensity, duration and/or frequency) with an increase in severity of at least 1 CCS class to at least CCS III

and

Severe recurrent ischemia requiring urgent revascularization: as defined by an episode of angina prompting the performance of coronary revascularization on the index hospitalization

or

An episode of recurrent angina after discharge that resulted in re-hospitalization

during which coronary revascularization was performed.

and

At least one of the following:

New or worsening ST or T segment changes on ECG. ECG changes should satisfy the following criteria for AMI in the absence of LVH and LBBB

ST Elevation - New ST elevation at the J point in two anatomically contiguous leads with the cut-off points: ≥ 0.2 mV in men (> 0.25 mV in men < 40 years) or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads.

ST depression and T-wave changes – New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or new T inversion ≥ 0.1 mV in two contiguous leads.

Evidence of ischemia on stress testing with cardiac imaging.

Evidence of ischemia on stress testing without cardiac imaging but with angiographic evidence of ≥ 70% lesion, and/or thrombus in the epicardial coronary artery or initiation/increased dosing of anti-anginal therapy.

Angiographic evidence of ≥ 70% lesion and/or thrombus in an epicardial coronary artery.

*Grading of Angina Pectoris According to Canadian Cardiovascular Society Classification

Class	Description of Stage
Class I	"Ordinary physical activity does not cause . . . angina," such as walking or climbing stairs. Angina occurs with strenuous, rapid, or prolonged exertion at work or recreation
Class II	"Slight limitation of ordinary activity." Angina occurs on walking or climbing stairs rapidly; walking uphill; walking or stair climbing after meals; in cold, in wind, or under emotional stress; or only during the few hours after awakening. Angina occurs on walking more than 2 blocks on the level and climbing more than 1 flight of ordinary stairs at a normal pace and under normal conditions.
Class III	"Marked limitations of ordinary physical activity." Angina occurs on walking 1 to 2 blocks on the level and climbing 1 flight of stairs under normal conditions and at a normal pace.
Class IV	"Inability to carry on any physical activity without discomfort—anginal symptoms may be present at rest."

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15.7 Definition of Heart Failure requiring Hospitalization

Heart failure requiring hospitalization is defined as an event that meets the following criteria:

Requires hospitalization defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 12 hour stay (or a date change if the time of admission/discharge is not available)

AND

Clinical manifestation of heart failure including at least one of the following: New or worsening:

dyspnea,

orthopnea,

paroxysmal nocturnal dyspnea,

edema,

pulmonary basilar crackles,

radiological evidence of worsening heart failure.

AND

Additional/increased therapy

Initiation of IV loop diuretic, inotrope or vasodilator therapy

Uptitration of IV therapy, if already on therapy

Initiation of mechanical or surgical intervention, or use of ultra-filtration, hemofiltration or dialysis that is specifically directed at the treatment of heart failure.

Biomarker results (e.g. brain natriuretic peptide) consistent with congestive heart failure will be supportive of this diagnosis.

15.8 Definition of New Onset Diabetes

The clinical definition of Type 2 diabetes consists of the following:

a. Presence of Fasting Plasma Glucose measured on two consecutive occasions ≥ 126 mg/dl (≥7.0 mmol/L) within 6 weeks (the Event Date will be the first of these two occasions)

Or

b. Presence of HbA1c measured on two consecutive occasions ≥ 6.5 % within 6 weeks in a laboratory which has validated compliance of a test that conforms to the National Glycosylation Standards Program (Little et al 2010) reference measurement of HbA1c (the Event Date will be the first of these two occasions)

Or

c. The institution and use of a diabetes medication for the purpose of glucose control by the patient including all oral agents, insulin, and injectable GLP-1 analogs. (the Event Date will be the Date noted on the prescription)

d. In the event wherein a patient has one laboratory parameter which would place them in the NOD category if repeated and confirmed within 6 weeks, then has a subsequent measurement another parameter which similarly would place them in the NOD category if repeated and confirmed within 6 weeks (e.g. FPG ≥ 126 mg/ dl (≥7.0 mmol/L) followed

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by HbA1c $\geq$ 6.5%, or vice versa) will be considered to have NOD (the Event Date will be the first of these 2 occasions).

15.9 Definition of Transient Ischemic Attack

A Transient Ischemic Attack is defined as change in the blood supply to a particular area of the brain, spinal cord, or retina, resulting in brief neurologic dysfunction that persists, by definition, for less than 24 hours

Symptoms and signs

New and focal neurologic sensory and/ or motor deficits, which have a rapid onset, last no more than 24 hours and resolve completely. Symptoms may be localized to brain, spinal cord, or retina, relative to the vascular supply affecting neurologic function.

Focal sensory, reflexes, and motor lesions, which are manifestations of the arterial structure from which the insufficiency arises. All new neurologic signs resolve completely within 24 hours from the time of onset.

- Hemiplegia/paresis
- Hemianaesthesia/sensory deficit
- Hemianopsia
- Neglect
- Isolated facial weakness/droop
- Ataxia/dysmetria
- Dysarthria/speech impairment
- Aphasia
- Other

Procedure

A CT , MRI, or MRA of the brain, which demonstrates no new pathology. A neurological or neurosurgical consultation may accompany the imaging study or studies, but is not required for the diagnosis of TIA.

15.10 Definition of Critical Limb Ischemia

Critical limb ischemia is a manifestation of occlusive peripheral arterial disease that describes patients with chronic occlusive disease who demonstrate ischemic rest pain or ischemic skin lesions (either ulcers or gangrene).

Symptoms

Pain at rest, claudication, recurrent skin lesions are common.

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Signs

Coolness to touch and pallor of the involved extremity may be present. Diminution or absence of pulse to palpation or bedside Doppler examination. Ulcers of the skin may be present.

Procedure

CT, MRI, MRA or angiography may be performed for diagnostic purposes. Angiographic or open revascularization may be attempted to improve arterial blood flow.

15.11 Definition of Limb Amputation due to Vascular Cause

Therapeutic resection of a limb or a portion of a limb due to a combination of vascular insufficiency, osteomyelitis, cellulitis / gangrene, or poor wound healing.

Symptoms

Symptoms may include claudication, rest pain, fever, recurrent infections. There may be a history of previous partial or complete amputations.

Signs

Decreased arterial pulse, abnormal temperature, deformity, chronic skin ulceration

Procedure

Therapeutic resection of the pathologic extremity. Reasons for amputation:

- Vascular insufficiency
- Osteomyelitis
- Cellulitis
- Gangrene
- Poor healing post-surgical wound
- Poor healing post trauma

15.12 Definition of Non-coronary Revascularization

Non-coronary revascularization is defined as vascular surgery or percutaneous intervention. Vascular surgery is defined as the placement of a conduit with or without proximal and/or distal anastamoses. Percutaneous intervention is defined as balloon inflation with or without stenting.

Symptoms

Symptoms will be specific to the arterial vasculature involved and the time of course of development of the occlusion(s).

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Signs

Signs will be specific to the arterial vasculature involved and the time of course of development of the occlusion(s).

Procedures

Diagnostic CT, MRI, MRA, or Doppler US may be performed.

Revascularization or attempted revascularization with or without stenting including carotid surgery, peripheral vascular surgery or PCI, including abdominal aortic aneurysm repair, carotid revascularization, femoral, popliteal iliac, renal, open or percutaneous peripheral interventions depending on the site definition of Supraventricular Tachycardia / Atrial Fibrillation

Supraventricular tachycardia includes abnormal sinus tachycardia, ectopic atrial tachycardia atrial fibrillation/atrial flutter (with rapid ventricular response) and junctional tachycardia.

15.13 Definition of DVT

Deep vein thrombosis is defined as the pathologic presence of thrombus with inflammation, which affects the leg veins (such as the femoral vein or the popliteal vein), the deep veins of the pelvis, or rarely an upper extremity vein.

Symptoms

There may be no symptoms referable to the location of the DVT, but the classical symptoms of DVT include pain, swelling and redness of the leg and dilation of the surface veins

Signs

DVT include pain, swelling and redness of the leg and dilation of the surface veins may be present. Homan’s sign, posterior calf pain on foot dorsiflexion may be present but is an insensitive indicator. Commonly, no signs are present.

Procedure

Duplex Ultrasonography is the most commonly used diagnostic test. Other tests may include d-dimer blood testing, CT with contrast, and infrequently venography. Confirmation by diagnostic study required.

15.14 Definition of PE

A Pulmonary Embolism is defined as an acute blockage of one or more pulmonary arteries by an embolus, which has originated elsewhere (usually venous thrombus) and traveled through the venous system to reach the pulmonary arteries.

Symptoms

Symptoms may include sudden-onset dyspnea, tachypnea), chest pleuritic chest pain, cough, and hemoptysis.

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Signs

In addition, severe cases can include signs such as cyanosis, tachycardia, hypotension, and syncope.

Procedure

Chest X-Rays may be performed but are rarely diagnostic. Blood testing for d-dimer is often used to screen prior to performing medical imaging. Spiral CT of the chest is often performed. If significant pathology makes spiral CT less useful, a ventilation perfusion scan of the chest may be available. Confirmation by diagnostic study and localization (left or right lung and lobe) required.

15.15 Definition of Coronary Angiography

Coronary angiography is an invasive procedure wherein radiocontrast dye is introduced via an arterial catheter into the aorta, left ventricle, and coronary arteries to examine the functional capacity and anatomy of these entities.

Procedure

A radiocontrast dye is administered as described above by a cardiologist or invasive radiologist, using peripheral access into an artery (femoral or brachial).

15.16 Definition of Coronary Revascularization

Coronary revascularization is an invasive procedure, which usually follows coronary angiography, wherein either Percutaneous Transluminal Intervention, followed by Stent Placement, Balloon Angioplasty, or CABG is performed to relieve obstructed coronary arteries.

Procedure

A team of medical professionals lead by either an invasive cardiologist (Percutaneous Transluminal Intervention, followed by Stent Placement, Balloon Angioplasty,) or a thoracic surgeon (CABG), who performs the described procedures.

15.17 Definition of SVT / Atrial Fibrillation

Supraventricular tachycardia includes abnormal sinus tachycardia, ectopic atrial tachycardia atrial fibrillation/atrial flutter (with rapid ventricular response) and junctional tachycardia.

Symptoms

Symptoms may include palpitations, dyspnea, chest pain, dizziness, numbness or loss of consciousness.

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Signs

Rapid heart rate, which may be regular or irregular. Peripheral pulses may be diminished or absent.

Procedure

ECG demonstrates narrow complex tachycardia originating from a site (or sites) above the ventricles. P waves may or may not be present, depending on the specific type of SVT.

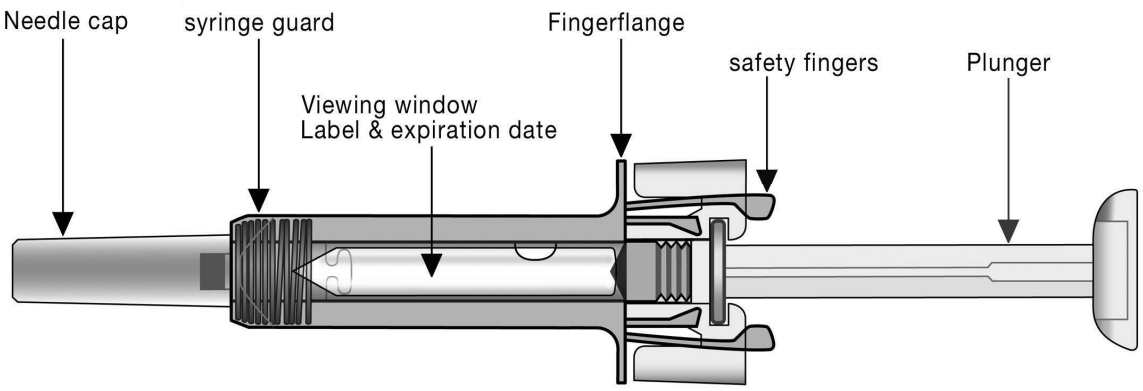
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16 Appendix 4 Instructions for use of the safety syringe

Before using the safety syringe, please read the following information carefully. The box contains pre-filled safety syringe(s) individually sealed in a plastic wrapper.

Parts of the safety syringe

This safety syringe consists of the actual prefilled syringe and a safety device type X100L (CE-marked and 510(k) K060743 cleared) from SafetySyringes, Inc.



This needle guard system is intended to aid in the protection of healthcare professionals, patients who self-inject doctor prescribed medications, and individuals that assist self-injecting patients form accidental needlesticks.

Important safety information

Caution: Keep the safety syringe out of the reach of children.

1. Do not open the sealed outer box until you are ready to use the safety syringe.
2. Do not use the safety syringe if either the seal on the outer box or the plastic wrapper is broken, as it may be not safe for you to use.
3. Never leave the safety syringe lying around where other might tamper it.
4. Be careful not to touch the Safety Fingers at any time. By touching them, the safety syringe may self-activate.
5. Do not remove the needle cap until just before you give the injection.
6. The safety syringe cannot be re-used. Dispose of the used safety syringe immediately after use in a sharps container OR according to the regulatory needs of your country.

Storage of the safety syringe

1. Store the safety syringe sealed in its outer box in the refrigerator between 2°C and 8°C (36°F and 46°F). DO NOT STORE IT IN THE FREEZER.

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2. Remember to take the safety syringe out of the refrigerator and allow it to reach room temperature before preparing it for injection (about 20 minutes).
3. Do not use the safety syringe after the expiration date shown on the outer box or syringe label. If it has expired, return the entire pack to the pharmacy.

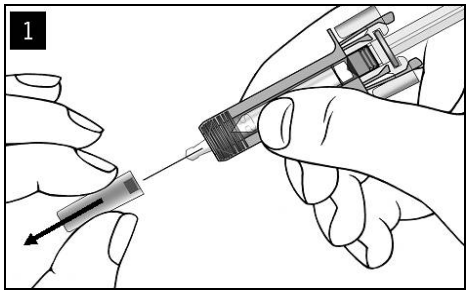
The injection site

The injection site is the place on the body where you are going to use the safety syringe. ACZ885 can be injected in either the upper outer thigh, abdomen or the upper outer arm. If you need more than one injection at a time, repeat the injection in the opposite thigh or arm.

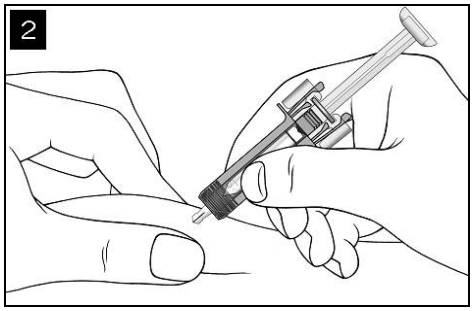
Preparing the safety syringe ready for use

1. Take the box containing the safety syringe out of the refrigerator and leave it unopened for about 20 minutes so that it reaches room temperature.
2. When you are ready to use the safety syringe, wash your hands thoroughly with soap and water.
3. Clean the injection site.
4. Remove the safety syringe from the outer box and take it out of the plastic wrapper.
5. Inspect the safety syringe. DO NOT USE if it is broken or if the liquid has a distinctly brown discoloration or contains particles. In all these cases, return the entire product pack to the pharmacy.

How to use the safety syringe

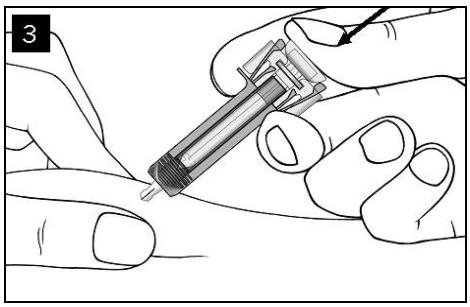


Carefully remove the needle guard from the safety syringe. Discard the needle guard



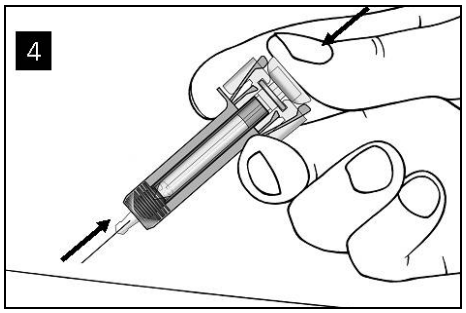
Gently pinch the skin at the injection site and insert the needle.

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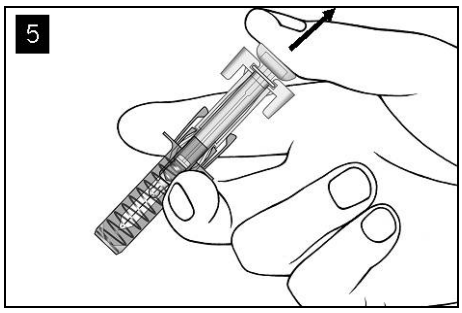


Holding onto the finger flange, **slowly** depress the plunger as far as it will go. If some drug leaks from the injection site, insert the needle further.

Keep the plunger pressed fully down while you hold the syringe in place for 5 seconds.



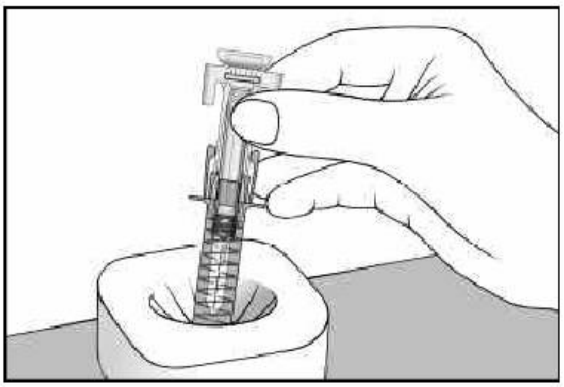
Keep the plunger fully depressed while you carefully lift the needle straight out from the injection site.



Slowly release the plunger and allow the syringe guard to automatically cover the exposed needle.

Disposal instructions

Dispose the used safety syringe immediately in a sharps container.



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Document History – Changes compared to previous versions of RAP module 3

Amendment 4, April 14, 2017

Section	Changes
2.1	Table 2-1: Addition of PD for site closure due to GCP non-compliance
2.2	Table 2.3-1 Age subgroup categories clarified to make clear that these are two separate subgroup variables
2.2	Table 2.3-1: Added subgroup as requested by FDA (presence of MI prior to index MI – yes/no)
2.2	Table 2.3-2 Change made Age subgroup categories to clarify this is two separate subgroup variables (consistent with Table 2.3-1)
2.3.1	Added text to highlight different terminology used in the protocol
2.3.8	Amended to reflect that the LPLV date will be used as the cut-off date since all events are planned to be adjudicated up to the last patients' visit
5	Removed Table 5-1. Revised text referencing table 5-1 to state that summaries should be based on the protocol visit schedule. Updated references to Table 5-2 due to table re-numbering.

Amendment 3, July 19, 2016

Section	Changes
Various	Various changes to text are made to clarify the intent. Minor changes are not reflected below. Changes that result in a change from what was originally intended are explained below.
1	Changed wording to reflect that the data from the washout and extension phases of the study will be addressed in a separate analysis plan and study report.
2.2	Table 2.3-3: removed subgroup related to patients entering washout who had stopped medication prior to final main trial assessment.
2.3.8	Clarifying that the analysis cutoff date could be earlier than the LPLV. In this case, events will only be considered as investigator reported.
2.3.9	- Removed planned sensitivity analyses for examining the assumption of non-informative censoring. This will be investigated, but not generally included in the study report. - Clarified that censoring date may not be the same for all time to event endpoints.
2.4	Figure 2-3 updated to match corresponding figure in study protocol.
5	Definitions of medication categories updated.
6	Removing the text about "post treatment phase" as it was resulting in confusion as to what was intended. Clarified main analyses will be based events occurring in the double blind phase.
6.1.2	Updated censoring algorithm to align with use of the cutoff date.
6.3.1	- Covariate adjusted analysis of primary endpoint changed to "may be considered." This is an exploratory analysis and not planned to be part of the study report. - Added that the association between hsCRP changes and outcomes will be explored, this is already mentioned in the current protocol.
6.3.2	- Added supportive analyses for diabetes related time to event endpoints. - Removed reference to analysis of washout period data.

Section	Changes
	- Added statement that washout period data will be analyzed in a separate study report or an addendum to the study report.
6.3.4	- Added text so that analyses will be dependent on number of events. - Removed text related to competing risks analysis.
6.5	Dose response model approach revised to reflect current plan for dose response modelling.
7	- Removed text related to summarizing data by trial part to avoid confusion between the main AE tables, which are pooled across trial parts and some specific analyses that present data separately by trial part. - Revised categories used for by-time-period analyses.
7.3.1	- Clarified on-treatment definition for AEs. - Removed plan for time-to-event analysis or AEs.
7.3.2	- Updated notable criteria in Table 7-1. - Added detailed description for analysis of long term effects on kidney function.
7.4	Updated list of adverse events of special interest to align with current safety profiling plan.
7.4.1	- Added by-time-period analyses for infections to align with other adverse event analyses. - Model for analysis of infections is revised to align with model for other adverse event analyses. - Analysis of duration of infections revised to only present a descriptive summary. Negative binomial model analysis is removed.
7.4.2	Removed ordinal regression analysis of LFT parameters; results are summarized using frequency tables.
7.4.3	Additional summary tables added to align with other adverse event analyses.
7.4.4	Removed summary of early drops in platelet counts.
7.4.8 – 7.4.12	- Topic of long term effects on kidney function was moved into Section 7.4.12 (Other safety topics). Analysis description is covered in section 7.3.2. (Laboratory data). - Topic of QT prolongation was moved into section 7.4.12 (Other Safety topics) and will be analyzed under section 7.3.4 (ECG). - Section on Hypoglycemia reordered to section 7.4.8. - Added new sections 7.4.9-7.4.11 (Autoimmunity reactions; Injection site reactions; Vertigo/dizziness). - Section on “Other safety topics” reordred to section 7.4.12. Section title changed to clarify that this section addresses other adverse events that are not part of the adverse events of special interest.
10	Removed; this will be addressed in a separate analysis plan and report.
11	Removed; this will be addressed in a separate analysis plan and report.
Appendix 1	Removed; this will be addressed in a separate analysis plan and report.
Appendix 2	Renumbered to Appendix 1.

Amendment 2, April 13, 2016

Section	Changes
Throughout	Editorial changes.

Section	Changes
2.1 (Table 2-2)	Updated Per protocol criteria.
2.2 (Table 2.3-1)	- Detail added on the region subgroups. - Clarified analyses would be done in all tables by region subgroup. - Updated definition of Pre-diabetic and Diabetic.
2.2 (Table 2.3-3)	- Details added to basis for diabetes diagnosis subgroups - Baseline HbA1c/FPG categories subgroups updated.
2.3.4	On-treatment definition added.
2.3.9 (previously 2.3.8)	- Added missing date imputation rules. - Amended time to event section. - MACE endpoint (and all individual components) censoring rules updated.
3.1	Changed the calculation of patient's age to be from date of start of screening instead of date of informed consent.
3.2	Updated sub-level categories.
5	- Added PCSK9 inhibitors to the list of non-statins. - Added SGLT2 inhibitors to the list of other oral hypoglycemic agents. - Added rules for the summary of statin use for the determination of the daily dose for each patient.
6.3.2	- Updated the definition of new onset diabetes. - Updated the second set of criteria for determining new onset diabetes.
6.3.5.1	Clarified that comparisons will be between each treatment and placebo.
6.3.5.3	- Clarified that change from baseline will be summarized. - Clarified that comparisons will be between each treatment and placebo.
6.3.5.6	Corrected the % missing cut off from more than 50% to 50% or more.
7.3.1	Amended the cut off for common events from 1% to 2%.
7.3.3 (Table 7-2)	Amended clinically notable changes in vital signs criteria.
7.4	Inserted table 7-3 with an updated list of AEs of special interest.
7.4.2	- Clarified baseline glycemic and abnormal LFT subgroup analyses. - Updated the covariates in the ordinal regression.
7.4.3	Amended the identification of malignancy.
12	Added references.

Amendment 1, June 26, 2014

Section	Changes
2.2	Updates to the per-protocol analysis sets.
2.2	Updates to the subgroup definitions.
2.3.2	Clarification of the hsCRP the baseline value.
3	Minor updates and clarifications to patient disposition, demographics, and medical history.
6.1.1	New section 6.1.1 was added for endpoint adjudication process.
6.3.1	- Addition of an additional early futility analysis to be performed at approximately 30% of the target number of 1400 patients have experienced CEC confirmed MACE, as per protocol amendment 8. - Clarification that in case one active arm is stopped, the target number of patients with a MACE that is still to be collected has to be adjusted. For

Section	Changes
	patients whose treatment arm is stopped per DMC recommendation, follow-up for cardiovascular (CV) and safety events will continue. - A sensitivity analysis will be performed by performing the primary analysis excluding all patients who were unblinded during the double blind phase of the study. - Change from baseline to the last hsCRP prior to the 1st confirmed MACE will be summarized by treatment.
6.3.2	- Clarification added that all identified cases of new onset of diabetes will be confirmed by the adjudication committee. - Clarifications on subgroup analyses for the key secondary new onset of diabetes endpoint.
6.3.4	Updates and clarifications to exploratory analyses.
6.3.5	Updates to SIS-16 (sub-section 6.3.5.6).
7	Several minor updates and clarifications.
8	Protocol amendment 8 introduced an additional early futility analysis to be performed at approximately 30% of the target number of 1400 patients have experienced CEC confirmed MACE.
12	Added new reference.

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Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) - A randomized, double-blind, placebo-controlled, event driven trial of quarterly subcutaneous canakinumab in the prevention of recurrent cardiovascular events among stable post-myocardial infarction patients with elevated hsCRP

Detailed Statistical Methodology

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List of acronyms

AE	Adverse event
AHD	Antihyperglycemic drug
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase (SGPT)
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical classification system
BCa	Bias-corrected and accelerated bootstrap
BMI	Body Mass Index
BNP	Brain Natriuretic Peptide
BWH	Brigham and Women's Hospital
CABG	Coronary Artery Bypass Graft
CAD	Coronary artery disease
CANTOS	Canakinumab Anti-inflammatory Thrombosis Outcomes Study
CCU	critical care unit
CDBL	Clinical Database Log
CEC	Clinical Events Committee
CHD	Coronary Heart Disease
CREDI	Novartis Clinical REsearch Documentation and Information system
CRF	Case Report Form
CV	Cardiovascular
DBL	Conjugated (direct) bilirubin
DBP	Diastolic Blood Pressure
DHP	Data Handling Plan
DILI	Drug-induced liver injury
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eGFR	estimated Glomerular Filtration Rate
FAS	Full Analysis Set
FPG	Fasting Plasma Glucose
HbA1c	Glycosylated hemoglobin
HDL	High Density Lipoprotein
HR	Heart Rate
hsCRP	high sensitivity C-reactive protein
ICU	intensive care unit
IDL	Intermediate density lipoprotein
Il-1β / Il-6	Interleukin-1β, Interleukin-6
IRT	Interactive Response Technology
IVRS	Interactive Voice Response System
LAD	Left Anterior Descending artery
LCX	left circumflex artery
LFT	Liver Function Test
LDL	Low Density Lipoprotein
LFT	Liver Function Test
LLN	Lower Limit of the Normal range
LPLV	Last Patient Last Visit
MACE	Major Adverse Cardiovascular Events (CV death, MI or stroke)
MAR	Missing At Random
MCMC	Markov chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
NMQ	Novartis MedDRA Query
NovDTD	Novartis Drug/Therapy Dictionary
NT-proBNP	N-terminal pro-Brain Natriuretic Peptide
OC/RDC	Novartis Oracle Clinical/Remote Data Capture system
PCI	Percutaneous Coronary Intervention
PD	Protocol Deviation or Pharmacodynamics
PG/PGx	Pharmacogenomic
PK	Pharmacokinetics
PPS	Per-Protocol Set
PT	MedDRA Preferred Term
QTc	heart rate-corrected QT interval
QTcB	QTc (Bazett's correction)
QTcF	QTc (Fridericia's correction)
RAAS	Renin-angiotensin-aldosterone system
RCA	Right coronary artery
RMP	Novartis Risk Management Plan
SAE	Serious Adverse Event
SAF	Safety Set
SBP	Systolic Blood Pressure
SMQ	Standardized MedDRA query
SOC	(primary) System Organ Class
SPP	Novartis Safety Profiling Plan
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TBL	Total bilirubin
TIA	Transient Ischemic Attack
TNF	Tumor necrosis factors
VAS	Visual analogue scale
VLDL	Very low-density lipoprotein

1 Introduction

The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS; Novartis study code CACZ885M2301) is a randomized, double-blind, placebo-controlled, event-driven trial of quarterly subcutaneous canakinumab in the prevention of recurrent cardiovascular events among stable post-myocardial infarction patients with elevated hsCRP.

This document outlines the agreements for the Statistical Analysis Plan for CANTOS based on the discussions between Brigham and Women's hospital and Novartis. The detailed statistical analysis plan including additional supportive/exploratory analyses, table shells and data set specifications will be prepared on this basis.

It is planned that after the completion of the double-blind treatment period patients will be followed in an open label follow-up study including re-starting canakinumab treatment, after they have completed the washout (or the main trial if they did not enter the washout). This safety follow-up study will collect safety events to be determined based on canakinumab profile in the main trial and major adverse cardiovascular events as defined in the primary endpoint of the main trial at bi-annual visits. Data from collected after the entry into this follow-up study will not be part of the main CANTOS clinical database (although the databases would subsequently have to be combined for analyses) and analyses using data from this follow-up study will not be specified in this document.

2 Definitions

2.1 Analysis sets

The following analysis sets will be defined for statistical analysis:

- **Screened set** – All patients who signed the informed consent.
- **Randomized set** – All patients who received a randomization number, regardless of receiving trial medication.
- **Safety set (SAF)** – All patients who received at least one dose of study drug and have at least one post-baseline safety assessment. Of note, the statement that a patient had no adverse events also constitutes a safety assessment. Patients will be analyzed according to treatment received. Treatment received will be considered identical to the randomized treatment if the patient has during at least one visit received the two injections constituting the treatment assignment at randomization.

  For patients who cannot be assigned in this manner, the most frequent dose at an individual visit (as defined in table 2-1) will be considered the treatment received. In the case of more than one equally frequent dose (ties), the highest most frequent dose will be assigned.

  Note: Any patient who did not receive any injection of study drug during the study is automatically excluded from the safety set, due to the lack of at least one dose of study medication.

Table 2-1 Definition of dose received at a visit

Sum of injection doses* [mg]	Dose at the visit
0 (meaning ≥ 1 placebo injections, but not even a partial canakinumab injection)	Placebo
> 0 to ≤ 50 mg of canakinumab	Canakinumab 50 mg
> 50 to ≤ 150 mg of canakinumab	Canakinumab 150 mg
> 150 of canakinumab	Canakinumab 300 mg

* Placebo injections counted as 0 mg

- **Full analysis set (FAS)** – All randomized patients. This is the primary efficacy population applied in all efficacy variables. Following the intent-to-treat principle, patients are analyzed according to the treatment they have been assigned to at the randomization. However, patients who have not been qualified for randomization and who have been inadvertently randomized into the study are excluded from FAS, provided these patients have not received study drug. (Note: The last part of the definition of the FAS is what is often referred to as misrandomized patients; i.e. patients for whom IVRS calls were made by the site either prematurely or inappropriately prior to confirmation of the patient's final randomization eligibility and double-blind medication was not administered to the patient. These patients would subsequently not continue to take part in the study or be followed-up. Misrandomized patients will not be included in the FAS, but they will be included in the Randomized Set. Further exclusions from the FAS may only be justified in exceptional circumstances; e.g., serious Good Clinical Practice violations).
- **Per protocol set (PPS)** – a subset of the FAS, consists of all randomized patients in FAS who take at least one dose of study medication and have no major protocol deviations affecting the primary analyses. Major protocol deviations leading to exclusion from PPS will be specified prior to database lock on a blinded basis and documented in a separate document. Data from patients discontinuing treatment will be censored a quarter year + 28 days after their last study drug injection.

All cases of prospectively defined protocol deviations will be identified prior to clinical database lock / unblinding and entered into a dedicated data panel as part of the locked database. Certain deviations may stipulate that only data up to the time of infraction will be included in the PP analysis, i.e. for analyses of the PP set data beyond this time-point will be ignored. This supplemental efficacy population is used to assess robustness of the primary analysis results. All exceptional cases and problems and the final decisions on the allocation of patients to populations will be fully defined and documented before data base lock (in particular before breaking the blind where applicable) and will be fully identified and summarized in the clinical study report as per the harmonized International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use tripartite guideline on statistical principles for clinical trials.

Criteria defining protocol deviations are provided in the Data Handling Plan (DHP). Protocol deviations will not lead to patient withdrawal from the study unless they indicate a significant risk to the patient's safety.

For the purpose of summarizing major protocol deviations, these will be considered to be those protocol deviations that lead to the exclusion from an analysis set. The current draft list of criteria leading to exclusions from analysis sets is shown in Table 2.2. Other currently foreseen protocol deviations will be reported in the clinical study report, but these will not lead to an exclusion from any analysis set. It is not currently foreseen that any criteria would lead to an exclusion from PPS from date of deviation.

Table 2.2 Criteria leading to exclusions from analysis sets

Analysis set	Criteria that cause a screened subject to be excluded
Screened	none
Safety (SAF)	Patients not receiving any dose of double-blind study medication
Randomized	Patient without a randomization number
	Subject was not randomized but took study drug (covered by the above)
Full Analysis Set (FAS)	Patient mis-randomized
	Patient without a randomization number
	Subject was not randomized but took study drug
Per Protocol set (PPS)	Patient mis-randomized
	Patient without a randomization number
	Subject was not randomized but took study drug
	Patients not receiving any dose of double-blind study medication
	Subject participates in any other investigational drug or device study or subject has received an investigational drug or device <= 30days of Visit 1 except for previous DES trial on countries with approved DES devices
	Major non-cardiac surgical or endoscopic procedure < 6 months prior to visit 1
	Major surgical procedure including PCI or CABG performed during the study but planned prior to randomization.
	CABG < 3 years prior to visit 1
	NYHA classification = Class IV
	Subject has a medical history of malignancy other than basal cell skin carcinoma
	Subject is currently (i.e. at randomization) taking a biological drug targeting the immune system (ie: TNF blockers, anakinra, rituximab, abatacept, tocilizumab)
	Date of Index MI < 30 days before randomization date
	Documented MI does not meet entry criteria or Date of most recent MI = blank but there is a visit 2
	Screening hsCRP < 2 mg/L or = blank
	Qualifying hsCRP measurement date < 28 days after date of prior PCI or Qualifying hsCRP measurement date < 28 days after date of qualifying MI
	Subject has not been on stable post MI meds for at least 4 weeks
Exclusion of data from PPS from date onwards	Data from patients discontinuing treatment will be censored a quarter year + 28 days after their last study drug injection.

2.2 Subgroup definitions

Data in general will either be presented separately by trial part or will be integrated using statistical models taking trial part and time since index MI into account. Additionally, especially safety data will typically be presented by randomization plan. These are not considered subgroups per-se, but are rather inherent in the trial design following protocol amendment 6 as discussed in section 2.4.

Generally subgroup analyses within a trial should be kept to a minimum. However, subgroup analyses need to be presented in submission documents like Summary of Clinical Efficacy, Summary of Clinical Safety, and Risk Management Plan and the clinical study report for the CANTOS trial will likely at least fulfill the first two of these roles.

The objective of the subgroup analyses is to evaluate the consistency of treatment effects across a wide variety of patient groups.

The primary composite (MACE) endpoint of CV death, nonfatal MI and nonfatal stroke, the key secondary variables and potentially other important efficacy variables will be analyzed for the subgroups shown in the Table 2.3-1.

Table 2.3-1 Subgroup analyses for the primary major adverse cardiovascular event (MACE) endpoint and other key efficacy outcomes

Subgroups	Definition
Age	<65, 65 to <75, ≥75 years
	Further subgroups may be determined based on baseline distribution after completion of recruitment
Sex	male, female
Race/Ethnicity	To be determined based on baseline distribution after completion of recruitment
BMI	To be determined based on baseline distribution after completion of recruitment
Region	To be determined based on baseline distribution after completion of recruitment; as many US and Canadian centers have started recruitment, a region that allows the assessment of efficacy in US + Canada will definitely be included
Glycemic status	Normoglycemic, pre-diabetic, diabetic
	Further subgroups may be determined based on baseline distribution after completion of recruitment
Smoking status	To be determined based on baseline distribution after completion of recruitment
Baseline hsCRP level	To be determined based on baseline distribution after completion of recruitment.
LDL-C level	To be determined based on baseline distribution after completion of recruitment.2. Tertiles of baseline LDL-C
SBP level	< 140 mmHg, ≥ 140 mmHg
	Further subgroups may be determined based on baseline distribution after completion of recruitment.
DBP level	< 90 mmHg, ≥ 90 mmHg
	Further subgroups may be determined based on baseline

Subgroups	Definition
	distribution after completion of recruitment.
Baseline statin usage/dose	To be determined based on baseline distribution after completion of recruitment.
Aspirin usage/dose	To be determined based on baseline distribution after completion of recruitment.
Medical history of gout	Yes / No
Cardiovascular risk factors	Diabetes mellitus (no, yes)
	Hypertension (no, yes)
	Dyslipidemia (no, yes)
	Multiple prior MIs (no, yes)
	Prior PCI (no, yes)
	Prior CABG (no, yes)
	Prior TIA/stroke (no, yes)
History of heart failure	Medical history meeting narrow Cardiac failure SMQ
eGFR	To be determined based on baseline distribution after completion of recruitment.
Time since index event	< 6 months post-index MI vs. ≥ 6 months post-index MI
Post-baseline hsCRP response/target levels achieved	To be determined based on baseline distribution after completion of recruitment – NOTE: careful interpretation of such a post-baseline subgroup will be needed

A set of standard safety subgroups shown in Table 2.3-2 will by default be looked at for selected safety analyses (see section 7).

Table 2.3-2 Standard safety subgroups

Subgroup	Definition
Age	<65, 65 to <75, ≥75 years
Sex	male, female
Race/Ethnicity	To be determined based on baseline distribution after completion of recruitment
Region	To be determined based on baseline distribution after completion of recruitment
Time since index MI	At least < 6 months vs. ≥ 6 months – what additional cuts are possible to be determined based on baseline distribution after completion of recruitment
BMI	To be determined based on baseline distribution after completion of recruitment
Co-existing medical conditions of interest (if enough patients): gout, diabetes (T2DM/T1DM)	To be determined based on baseline distribution after completion of recruitment
hsCRP level (incl. e.g. very high values)	To be determined based on baseline distribution after completion of recruitment

In addition to the two preceding sets of subgroups those specified in Table 2.3-3 will be used in some analyses as stated in the relevant analysis plan sections. They are shown here irrespective of what kind of analysis they will be used for to highlight that they needed to be included in analysis datasets.

Table 2.3-3 Additional subgroups needed only for specific analyses

Subgroups	
Duration of diabetes	To be determined based on baseline distribution after completion of recruitment
Basis for diabetes diagnosis	Laboratory criteria (FPG ≥ 126 mg/dl; HbA1c ≥ 6.5%) Only medical history or anti-diabetic medication use (non-diabetic patients are not classified)
Baseline HbA1c/FPG categories	To be determined based on baseline distribution after completion of recruitment
Quintiles of baseline HbA1c in pre-diabetics	Quintiles of baseline HbA1c only amongst those with pre-diabetes
Quintiles of baseline FPG in pre-diabetics	Quintiles of baseline FPG only amongst those with pre-diabetes
History of macular degeneration	Medical history or use of relevant medications
Baseline neutrophil levels	To be determined based on baseline distribution after completion of recruitment.
Baseline use of antithrombotic medications	Yes/No – Identified via ATC codes/terms
key drugs for the trial population affected by CYP450 with a narrow therapeutic index (e.g. warfarin and amiodarone)	Yes/No – Identified via ATC codes/terms
Vaccines within 3 months	Yes/No – Identified via ATC codes/terms
Vaccines	Yes/No – Identified via ATC codes/terms
Medical history of gout, rheumatoid arthritis or other inflammatory diseases such as lupus or psoriatic arthritis	Yes/No
History of malignancy	Yes/No
Baseline QTcF	Elevated or normal
Baseline heart rate	< 55 bpm versus ≥ 55 bpm
Alcohol history	To be determined based on baseline distribution after completion of recruitment.
Baseline platelet counts	To be determined based on baseline distribution after completion of recruitment.
Early drops in platelet counts (or thrombocytopenia)	To be determined based on observed distribution after completion of recruitment.
Early drops in neutrophils (or neutropenia)	To be determined based on observed distribution after completion of recruitment.
Patients that entered the washout but had stopped study medication prior to the final main trial assessment.	See subgroup description

To support regional submission activities and health authority interactions, at a minimum the subgroups shown in table 2.3-4 are needed.

Table 2.3-4 Regional/country subgroups to support regional/local submissions, for which selected tables have to be repeated

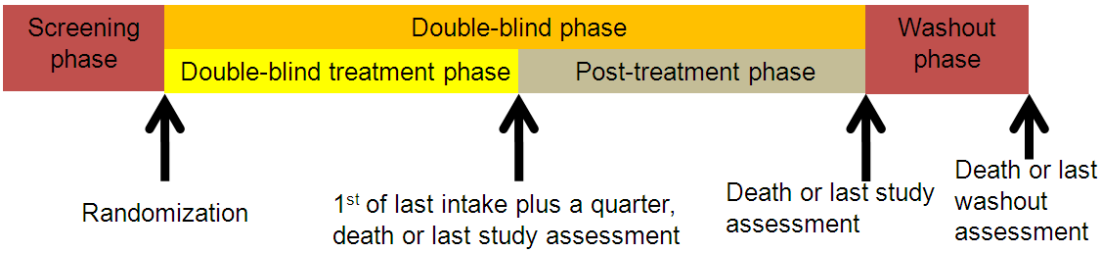
Preliminary* list of variable(s) / analyses to be repeated	Regional/country subgroup
On FAS	1. Japan
Disposition/Demography/Patient and disease characteristics	2. Japan and Korea
Incidence of primary endpoint	3. Mainland China (if participating in the study)
Incidence of key secondary endpoints	4. Mainland China + Taiwan (if both participating in the study)
Incidence of secondary endpoints (includes death)	5. Asian patients/Rest of World
Analyses of other selected efficacy variables (e.g. hsCRP)	6. India
On SAF	
Adverse events by system organ class and preferred term	
Serious adverse events by system organ class and preferred term	
Deaths	
Standardized MedDRA queries	
Adverse events of special interest	

* subject to changes dependent on local requirements

2.3 Assessment windows, baseline and post baseline definitions, missing data handling

2.3.1 Assessment windows and visit mapping

Figure 2-1 Assessment windows



Screening phase

The screening phase is defined as the period prior and up to randomization. After obtaining written informed consent, the subject will be evaluated for eligibility to participate in to the study.

Double-blind phase

The double-blind phase includes double-blind treatment phase and post-treatment phase. It does not include the washout phase or any long-term follow-up after the completion of this trial.

Double-blind treatment phase

The double-blind treatment phase refers to the time period during which patients actually receive treatment (or are still expected to have significant PK exposure).

The double-blind treatment phase begins at the time of randomization and ends with the earliest of the last trial drug intake plus a quarter year (91 days), the death of the patient or the last study assessment in the main part of the trial (i.e. excluding the washout). During the double-blind treatment phase, subjects will return for scheduled clinic visits.

Post-treatment phase

The post-treatment phase refers to the time period during which patients no longer receive treatment and no longer have significant PK exposure. As this is an outcome trial, patients should nevertheless be followed-up during this phase until the end of the trial or their death, in order to assess the occurrence of trial endpoints.

The post-treatment phase (after unscheduled drug discontinuation or study completion/termination) begins after last trial drug intake plus a quarter year (91 days) + 1 day and ends with the last study assessment (in the main part of the trial; i.e. not including the washout) or the death of the patient. During the post-treatment phase, subjects should also continue to return for scheduled clinic visits.

The distinction between double-blind treatment phase and post-treatment phase does not affect the primary intention-to-treat analysis, but affects e.g. the supportive on-treatment sensitivity analysis.

Washout phase for pre-diabetics

Pre-diabetics who have not yet progressed to diabetes at the end of this trial will first enter into the 6 month washout phase. The purpose is to help elucidate whether a reduction in diabetes diagnoses in the main trial was due to a modification of the disease progression or solely due to glucose-lowering not persisting after the discontinuation of study drug. This washout phase will be considered to start with the study completion visit for the main trial and end with the completion visit for the washout, the patient's death prior to such a visit or the patient being lost to-follow-up prior to such a visit.

Primary endpoints occurring in the washout phase will not be part of the primary analysis for this trial.

2.3.2 Baseline definition

Baseline is defined as the last available measurement during the screening phase, i.e. prior and up to randomization. That means that if the measurement at the baseline visit is missing, then the previous measurement preceding baseline will be used as the baseline measurement.

For hsCRP in case of multiple assessments prior to randomization the baseline value will be the mean of the available hsCRP values prior and up to randomization.

2.3.3 Post-baseline definition

Post-baseline is defined any assessment after randomization including treatments and outcomes that occur after but on the same day as randomization. On the other hand, measurements and laboratory samples taken on the day of randomization during the randomization visit (at the end of which a subject is randomized) are considered baseline assessments.

2.3.4 Visit mapping for the study completion visit

As the study completion visit will occur after a different length of follow-up for different patients, it needs to be defined for which scheduled timepoint assessments at the study completion visit are counted. I.e. it needs to be defined when e.g. plotting the quarterly/bi-yearly hsCRP values over time, whether the study completion hsCRP should count for the 0.25 year visit, the 0.5 year visit, the 0.75 year visit, the 1 year visit etc., which will be based on when it occurred.

When showing values over time, study completion visit assessments will be displayed as if they had occurred at the next scheduled timepoint for that assessment. For example, if a patient has a regular month 45 visit and then the study completion visit occurs 2 months later, then the study completion visit would be considered to provide the patient's values for month 48.

2.3.5 Data from unplanned visits and unscheduled visits

Data from unplanned visits and unscheduled visits will not be re-mapped to other visits for the purpose of displaying variables over time. Such data will however be included in time windows for the assessment of endpoints (e.g. new onset of diabetes), counted towards shift tables or other analyses regarding the worst observed values for patients.

2.3.6 Time windows for new onset of diabetes and other laboratory based time to event variables

Laboratory based endpoints will be classified by whether they occurred in certain time windows according to the assessment schedule as shown in the tables below. If the endpoint has already been assessed in the same time window (only if this was at a regularly scheduled visit according to the assessment schedule), then events based on the study completion visit will be considered to have occurred in the next time window.

Table 2-4 Time windows for endpoints based on HbA1c, FPG, standard hematology, biochemistry or fasting lipid profile

Time window	Start of time window (study days)	End of time window (study days)
Week 2 visit	1, but only after the laboratory assessment of the baseline visit	28
Month 1.5 visit	29	68
Month 3 visit	69	137
Month 6 visit	138	228
Month 9 visit	229	320
Month 12 visit	321	457
Month X visit (where X≥18 is a multiple of 6)	Rounded [(365.25 / 12) * (X – 3)] + 1	Rounded [(365.25 / 12) * (X + 3)]

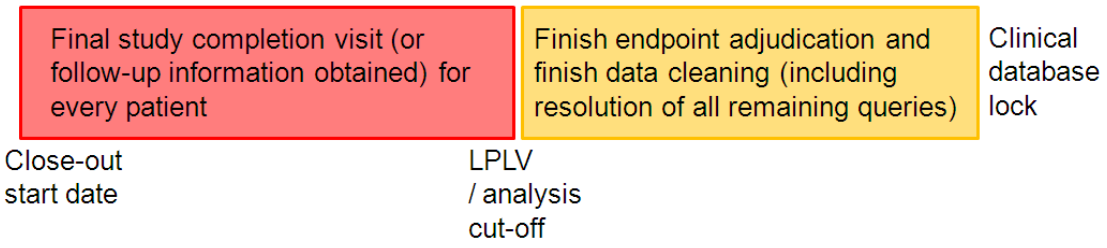
Table 2-5 Time windows for urinalysis based endpoints

Time window	Start of time window (study days)	End of time window (study days)
Month 3 visit	1, but only after the laboratory assessment of the baseline visit	228
Month 12 visit	229	639
Month 30 visit	640	1096
Month 42 visit	1097	1461
Month X visit (where X≥42 is a multiple of 12 added to 30)	Rounded [(365.25 / 12) * (X – 6)] + 1	Rounded [(365.25 / 12) * (X + 6)]

2.3.7 Close-out procedure

CANTOS is designed as an event driven trial with the aim to finish the trial when approximately 1,400 patients had a confirmed primary endpoint. A close-out procedure will be initiated with a timing appropriate to achieve this.

Figure 2-2 Overview of close-out procedure



The aim of the close-out procedure will be to allow for all necessary activities (like study completion visits, data cleaning, raising and resolution of all queries to the clinical sites, etc.) including endpoint adjudication for endpoints that occurred during the study and prior to final visit/analysis cut-off, whichever occurs first.

The close-out procedure will start on a close-out start date, with final patient visits occurring until the date of the last visit of the last patient (LPLV), which will also be the analysis cut-off date (see censoring algorithm), and finish with the clinical database lock.

It will be attempted to follow each patient until a final study completion visit between the close-out start date and the analysis cut-off date unless the patient died. If a patient does not attend the final visit in person, there will be attempts to obtain information by other means between the close-out start date and the analysis cut-off date; this information will be available under the final study completion visit.

For patients who withdrew consent, the follow-up information such as vital status and whether endpoints occurred ("yes", "no", "unknown") will still be collected during the close-out period to the maximum extent possible under local regulations.

Events occurring after the analysis cut-off date but before a patient's final visit, (in the case where the final visit could not be performed by the analysis cut-off date) will not require adjudication. Similarly events occurring after the final visit, but before the analysis cut-off, e.g. for patients that entered the long-term follow-up or the washout, will not be entered as endpoints into the database for the main trial.

2.3.8 Missing data handling

Time-to-event variables

Regarding time-to-event variables only observed/reported events will be used in the analysis – i.e. for censored patients no events will be somehow imputed (except for in some sensitivity analyses). This means that in the primary analysis censoring of non-observed events will be assumed to be non-informative. Sensitivity analyses with respect to this assumption will be performed. Incomplete dates of events and censoring dates will be imputed as described below.

In the primary analysis, all patients, including those who discontinue study therapy due to lack of efficacy, adverse events or abnormal laboratory values, will be followed until death or the end of the study. Information on patients discontinuing study drug or participation in trial visits will be collected whenever possible and will be used in the analysis. In patients who could not be followed up for primary outcome events, it is aimed to at least determine the vital status of the patients at the final visit.

In general, every effort will be made to collect information about the primary outcome events for those patients who discontinued treatment or their participation in the trial. In patients who could not be followed up for primary outcome events, it is aimed to at least determine the vital status of the patients at the final visit.

The following rules will be applied separately for the composite MACE endpoint and for all its individual components. Patients who have not experienced the respective endpoint will be censored on the date of the last follow-up in the following way:

- for patients who die, the censoring date will be the date of death unless the patient withdrew his consent for the collection of follow-up information,

- for patients who attend a final visit during close out, the censoring date will be the final visit date,
- otherwise the censoring date will be based on the last visit at which the investigator reported that it was known whether the patient experienced any clinical events since the last visit (i.e. answer of "yes" or "no" to this question, not "unknown"). The last known date the patient was reported alive **at that visit** will be used. If the last known date the patient was alive is missing the date of the last visit at which it was known whether the patient experienced any clinical events since the last visit will be used.

Should the censoring date lie after the chosen analysis cut-off date, it will be set to the analysis cut-off date. Note that this censoring date should be derived independently of any specific analysis, because it will be used to describe the extent of follow-up for (potentially multiple) cardiovascular events and for multiple different time-to-event analyses (e.g. time to MACE, time to MI, analyses of multiple cardiovascular events).

If the date of a MACE endpoint or of censoring is not known or is incomplete following all attempts to get an approximate date, a day will be imputed using the following algorithm:

- If only the month of the event is known, then the 15th day of this month will be imputed.
- If only the year of the event is known, then the 1st July will be imputed.
- If year, month and day are unknown, the event date will be imputed as the randomization date and the patient will be assumed to have had a MACE event post-randomization on day 1 of the follow-up.
- If this imputation rule leads to a date before the randomization date or after a patient's last study visit or after a patient's death, but the date could have been on one of these dates, then the even date will be imputed to be the one out of these dates that the incomplete date is consistent with.
- In the first three bullet points it will also be taken into account, whether it is known that a patient was event free up to a certain time. If that is the case the imputed date will be restricted to be after the date up to which the patient was event free, unless this is incompatible with the incomplete date or violates the 4th bullet point.

Date of trial drug injection

In case of missing information on the day of injection of any study medication the date of the corresponding dispensing visit will be used as date of injection. If that is missing the date foreseen for that visit in the protocol will be assumed.

Other missing data

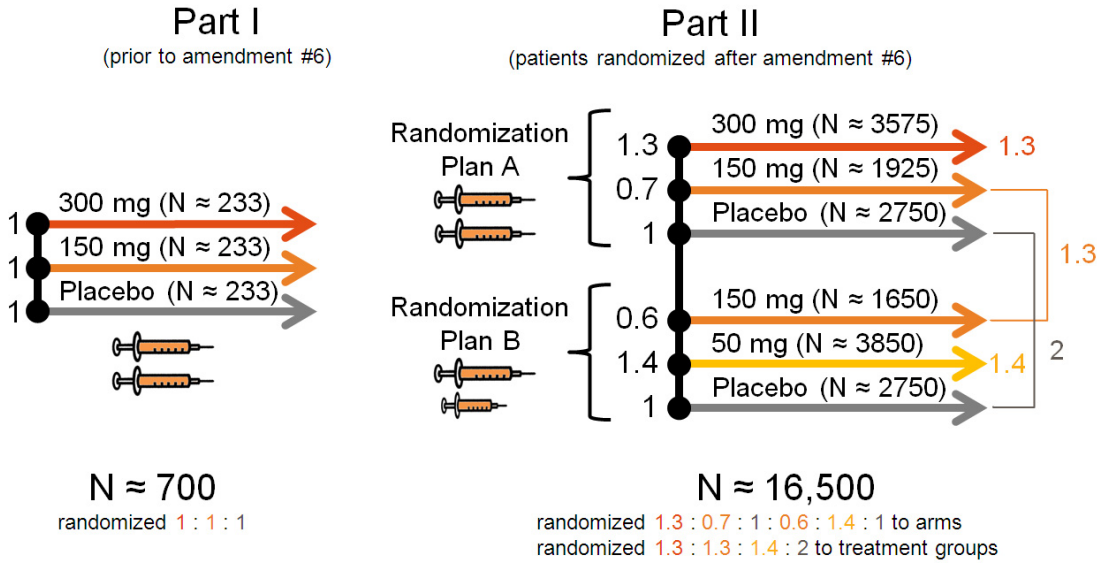
Missing laboratory, vital signs, ECG, quality of life and other data will not be imputed for the purpose of summary statistics. Such summary statistics will be displayed longitudinally showing only those values that are available. Subsequent more in-depth analyses may explore other approaches and appropriate data imputation methods will be chosen for each type of analysis.

2.4 Key trial design aspects relevant to trial analysis

Randomization and blinding

Initially, patients were randomized in a 1:1:1 fashion to 300 mg canakinumab with induction dose, 150 mg without an induction dose or placebo quarterly. Following Health Authority feedback on the doses a lower 50 mg dose arm was added in protocol amendment 6 in order to examine the dose response of canakinumab in preventing recurrent cardiovascular events, and to determine if a dose lower than 150 mg would have a favorable risk benefit ratio. Following this amendment, randomized allocation to the four trial arms was to be unbalanced in order to optimize power, now that three active arms were compared versus a common control arm.

Figure 2-3 Patient allocation to treatment arms prior and after protocol amendment 6



Following implementation of protocol amendment 6 all new patients are randomly assigned to 1 of 6 trial arms, while the approximately 700 patients expected to be randomized prior to the amendment continue in the arm to which they were previously randomized.

Prior to protocol amendment 6, the following two presentations of canakinumab solution for injection in pre-filled syringes are used in CANTOS:

- Canakinumab 150 mg/1 ml, and
- Placebo matching canakinumab 150 mg/1 ml

In addition, the following pre-filled syringes were available to be used for the purpose of implementing the 50 mg arm following amendment 6:

- Canakinumab 50 mg/0.5 ml, and
- Placebo matching canakinumab 50 mg/0.5 ml.

Canakinumab 50 mg/1 ml pre-filled syringes that fully match 150 mg pre-filled syringes were not available near the time of protocol amendment 6. Thus, in order to evaluate 300 mg, 150 mg and 50 mg versus placebo in a fully blinded fashion, a triple-dummy design with 3

injections per visit would have been required. As feedback from investigators indicated that this would constitute an unacceptable burden to patients we identified the approach shown in Figure 1-1 as the most appropriate solution for introducing the 50 mg dose into the CANTOS trial.

For the three trial arms in Randomization Plan A, study drug will consist of two injections of canakinumab 150 mg/1 ml or the matching placebo, while the three trial arms in Randomization Plan B study drug will consist of one injection of canakinumab 150 mg/1 ml, or the matching placebo and one injection of canakinumab 50 mg/0.5 ml, or the matching placebo. While investigators will be able to deduce from the size of the pre-filled syringes whether a patient is in Randomization Plan A or B, the chance that the patient is on active treatment is the same in either case (2:1). I.e. they are fully blinded with respect to active treatment or placebo, but can rule out one of the three possible active doses in case the patient were to be on active treatment.

As a result, the pre-specified primary analysis described in detail in section 6.3 comprises both

1. a randomized contrast between groups that are completely double-blind versus each other (canakinumab 150 mg versus placebo) and veiled versus the other groups and
2. two randomized contrasts between groups that are veiled (canakinumab 300 mg versus placebo and 50 mg versus placebo).

The term veiled is used in the sense of Senn (Senn 1995), who defines a veiled trial as a trial in which a patient's treatment group is not known, but the possibilities can be narrowed down to a subset of all existing treatment groups in the trial - in CANTOS every patient can clearly only be in 3 out of the 4 trial arms, either a patient can be on canakinumab 300 mg, 150 mg, or placebo or the patient can be on canakinumab 150 mg, 50 mg or placebo.

As far as combining data from trial part 1 and trial part 2 is concerned, the pre-specified analysis preserves the double-blind nature of the contrast in the same way that a patient-level (network) meta-analysis would. This is done by not making any direct comparisons between patients in trial part 2 and those in trial part 1 - i.e. no naïve pooling of patients across trial part, which would have been inappropriate, because patients were not concurrently recruited for the two trial parts and assignment to trial part was not at random. Instead, for example the 50 mg dose in trial part 2 can only be compared to the placebo group in trial part 1 indirectly using a double contrast by combining the 50 mg versus 300 mg and 50 mg versus 150 mg contrasts in trial part 2 with the 300 mg versus placebo and 150 mg versus placebo contrasts in trial part 1. As discussed by Senn, estimates obtained in this way have a substantially higher variance than the direct single (potentially biased) contrast (Senn 2008). Comparisons between treatments randomized to Part II on the other hand pool all concomitantly randomized arms because the potential bias is considered to be too small to justify the loss in efficiency incurred by such an approach. Furthermore, it was decided that any hypothetical bias could be handled for several reasons. Firstly, because patients are randomly assigned to the two randomization plans, one can expect patients in randomization plan A and B to be comparable at baseline. Secondly, any possible bias is expected to be small, if it exists. While investigators and patients can potentially identify whether patients are either on 300 mg, 150 mg, or placebo (trial part 1 or randomization plan A in trial part 2) or alternatively on 150 mg, 50 mg, or placebo (randomization plan B in trial part 2), the odds of a patient being on active

treatment are the same in either case (2:1). In either case the number of potential treatment groups is only narrowed down to a limited extent, namely from 4 to 3. Taken together, this makes it unlikely that any influence of this knowledge on investigators and patients would have any substantial impact with respect to e.g. patient management, follow-up or endpoint reporting. Thirdly, whether this is the case can be confirmed at the end of the trial due to the presence of both a placebo arm and a 150 mg arm in both randomization plans. For this purpose the placebo groups in randomization plans A and B will be compared against each other, the 150 mg groups in randomization plan A and B will be compared and the 150 mg versus placebo contrasts will be compared between randomization plan A and B.

3 Patient disposition, background and demographic characteristics

3.1 Patient disposition

The number of patients screened, randomized and included in the full analysis set (FAS) will be presented by treatment group and overall for the screened set, as well as by trial part. For the screened set the reasons for screen failures will be tabulated. The number and percentage of subjects in the randomized set who completed the study, who discontinued the study (lost to follow-up, subject/guardian decision, technical problems, death) and the reason for discontinuation will be presented for each treatment group and all patients, as well as by trial part. The frequency (%) of patients with protocol deviations as well as the criteria leading to exclusions from analysis sets will be presented in separate tables for the randomized set. Finally, the number of enrolled and randomized patients by region (see section 2.2) as well as the number of patients enrolled and randomized per region and country will be presented descriptively for the randomized set overall and by trial part.

When the exact date of birth cannot be collected for data privacy reasons, the year of birth is collected instead and the patient's age is imputed by the Oracle Clinical Remote Data Capture system (OC/RDC) on that basis. For that purpose OC/RDC assumes the patient's birthday to have been on 1 July of the year and calculates the patient's age as the number of days between that day and the date of informed consent divided by 365.25.

3.2 Background and demographic characteristics

The following common background and demographic variables will be summarized using descriptive summary statistics (for continuous variables mean, median, standard deviation, Q1 (25th percentile), Q3 (75th percentile), minimum and maximum and for categorical variables frequency and percentage):

- Age [years]; age categories <65, 65 to <75, ≥75 years
- Sex (male/female)
- Race (Caucasian, Black, Asian, Native American, Pacific Islander, Unknown, Other) and Ethnicity (Hispanic, East Asian, Southeast Asian, South Asian, West Asian, Russian, Mixed ethnicity, Not reported, Unknown, Other)
- Height [cm]
- Weight [kg]

- Body mass index [kg/m^2] calculated as weight [kg]/ $height^2$ [m^2]; BMI categories of normal, overweight or obese
- Waist circumference [cm]
- Sitting pulse [bpm]
- Mean sitting SBP [mmHg]; additionally tertiles and categorization of < vs. ≥ 140 mmHg
- Mean sitting DBP [mmHg]; additionally tertiles and categorization of < vs. ≥ 90 mmHg
- Controlled baseline blood pressure (msSBP < 140 mmHg and msDBP < 90 mmHg)
- Smoking history (What is the subject's usage status? Never/Current/Former)
- Alcohol history (amount consumed on average per day <1, 1 to 2, >2 to 3, >3 to 4, >4 to 5, >5 or more)
- Region of enrollment providing a detailed break-down (North America, Middle America, South America, Western Europe, Northern Europe, Russia, Ukraine and Baltic countries, Eastern Europe, Southern Europe and Mediterranean countries, South Asia, China and Taiwan, Japan and Korea, Southeast Asia, Australian Continent, Other) – other analyses may use appropriate groupings based on the character of the analysis
- Cardiovascular risk factors and other co-morbidities (as per protocol solicited events CRF, unless otherwise specified):
  - Glycemic status (T2DM, T1DM, pre-diabetes, normoglycemic; MedDRA terms to identify T1DM will be pre-specified)
  - Complications of diabetes
    - Diabetic retinopathy (Diabetic proliferative retinopathy/Diabetic non-proliferative retinopathy)
    - Diabetic nephropathy
    - Diabetic neuropathy
    - Diabetic foot ulcers
  - Hypertension
  - Dyslipidemia/Hyperlipidemia
  - Prior TIA/stroke
    - Prior Transient Ischemic Attack
    - Prior Hemorrhagic Stroke
    - Prior Ischemic Stroke
    - Prior Stroke of unknown type
  - Atrial fibrillation
  - Supraventricular tachycardia
  - Deep Vein Thrombosis
  - Pulmonary embolism
  - Peripheral Arterial Disease

  - Prior repeated MI (multiple MIs identified via narrow Myocardial infarction SMQ in medical history)
  - Prior PCI (from the Prior Coronary Revascularization Procedures CRF)
  - Prior stent implantation (incl. drug eluding stent or bare metal stent; from the Prior Coronary Revascularization Procedures CRF)
  - Prior CABG (from the Prior Coronary Revascularization Procedures CRF)
  - Heart failure (identified in Medical History using narrow Cardiac Failure SMQ)
- Medical history of gout (as per protocol solicited events CRF)
- Medical history of macular degeneration (list of MedDRA terms to be pre-specified)
- Time since index MI: summary statistics and classification into
  - < 6 months post-index MI sub-classified into
    - <30 days,
    - 30 days to 3 months (≤91 days)
    - 3 months (>91 days) to 6 months (<183 days)
  - ≥ 6 months post-index MI sub-classified into
    - 6 months (≥183 days) to 1 year (≤365 days)
    - 1 year (> 365 days) to 2 year (≤731 days)
    - 2 (>731 days) to 3 years (≤1096 days)
    - 3 (>1096 days) to 5 years (≤1826 days)
    - 5 (>1826 days) to 7 years (≤2557 days)
    - 7 (>2557 days) to 10 years (3653 days)
    - > 10 years (>3653 days)
- hsCRP [mg/L] (two values available with the mean of these two used in analysis)]; tertiles, categories <3 mg/L, 3 to < 4 mg/L, ..., 9 to < 10 mg/L, ≥ 10 mg/L
- HbA1c [%]; categories <5.7%, 5.7 – 6.4%, 6.5 to 7.4%, ≥ 7.5%
- FPG [mmol/L]; categories <5.6 mmol/L (100 mg/dL), 5.7 mmol/L to 6.9 mmol/L (100 to < 126 mg/dL), 7.0 to 11.0 mmol/L (126 to < 200 mg/dL) and ≥ 11.1 mmol/L (200 mg/dL)
- Lipid profile: continuous, as well as LDL-C tertiles, LDL-C <70 mg/dL vs. ≥ 70 mg/dL (1.8102 mmol/L), tertiles of HDL-C
- eGFR [mL/min/1.73m^2]; categories < 30, ≥30 to <60, ≥60 to <90 and ≥90 mL/min/1.73m^2
- Level of exercise (rarely/never, less than once a week, once a week, 2-3 times a week, 4-6 times a week, daily)
- Family history of MI, stroke, diabetes or premature coronary artery disease (No / Yes with sub-categorization by age at first event)
- Highest level of education (0 years, 1-4 years, 5-8 years, 9-12 years, 13-16 years, >16 years)
- Medications used at the time of randomization will also be summarized (see section 5)

For purely descriptive purposes, treatment group comparability will be examined using the Cochran-Mantel-Haenszel test stratified by time since index MI (< vs. ≥ 6 months) for the categorical variables and the F-test with time since index MI (< vs. ≥ 6 months) as a categorical covariate for the continuous variables as appropriate. These p-values will be provided for descriptive purposes and will not be considered to define any formal basis for determining factors that should be included in statistical models. Any concerns about imbalances between treatment groups are already addressed by the pre-specified sensitivity analyses that assess the treatment effects adjusted for pre-specified potentially prognostic covariates (see Section 6.3).

The eGFR is calculated using the MDRD formula. eGFR [mL/min/1.73 m^2]=175 × (serum Creatinine [umol/L]/88.4)$^{-1.154}$ × (age [years])$^{-0.203}$ × (0.742 if female) × (1.212 if African American) (Levey et al. 2007).

3.3 Medical History

Any condition entered on the *relevant medical history / current medical conditions* CRF will be coded using the MedDRA dictionary. Frequency tables will be provided by primary system organ class, preferred term (as well as per standardized and Novartis MedDRA queries) and treatment group.

Adverse events occurring between screening and baseline will also be reported as medical history, but additionally reported separately as adverse events occurring between screening and baseline.

4 Study medication

The duration of the double-blind treatment phase will be computed as the time from the first injection to the first out of

1. the last injection date plus a quarter year (91 days),
2. the patient's death
3. the patient's study completion visit during the study close-out period
4. or the analysis cut-off.

This algorithm reflects the planned treatment schedule and the long half-life of the study drug. Missing dates in this algorithm will be imputed in the same way as missing dates for time-to-event analyses.

The duration of the post-treatment phase will be computed as the number of days from the day after the end of the double-blind treatment phase to the end of the post-treatment phase. If the end of the double-blind treatment phase coincides with the end of the double-blind phase, then the duration of the post-treatment phase will be 0 days.

The duration of the double-blind phase, double-blind treatment period and post-treatment phase will be summarized for the FAS and SAF by treatment group descriptively including by duration categories. Overall patient-years will also be displayed and will be computed as the sum of patient days for all patients divided by 365.25.

Duration of exposure to study treatment excluding interruptions will be computed and summarized as above for the SAF, but not counting periods during which the last injection was more than a quarter year ago.

5 Concomitant medication

Prior or concomitant medications will be summarized for the safety set in separate tabulations based on the coding dictionary used. Medications will be presented in alphabetical order, by preferred terms and grouped by anatomical main group. Tables will show the overall number and percent of patients receiving at least one drug of a particular preferred term and at least one drug in a particular anatomical main group.

Prior medications and significant non-drug therapies are defined as any medications and significant non-drug therapies taken prior to the randomization visit. Concomitant medications and significant non-drug therapies are defined as those used during the double-blind phase. Concomitant medications that were prohibited as per protocol and given during the conduct of the study as well as significant non-drug therapies will be summarized.

Furthermore, classes of medications to be precisely defined in a separate Excel file that will be stored in the Novartis CREDI system, will be summarized separately. These will include classes such as the following:

- Anti-ischemic agents
  - Beta blockers
  - Intravenous or oral nitrates
  - Calcium channel blockers
- Antithrombotic agents (excluding antithrombotic intravenous and subcutaneous drugs intended for acute setting such as abciximab, eptifibatide, or tirofiban, which are not expected to be used chronically and are consequently less relevant in this population – these will be reported separately in the Clinical Study Report)
  - Acetylsalicylic acid (aspirin)
  - Non-aspirin oral anti-platelet agents
    - P2Y12 inhibitors (like clopidogrel, ticagrelor and prasugrel)
  - Direct Thrombin Inhibitors
  - Other antithrombotic agents (e.g. anticoagulants)
- Renin-Angiotensin-Aldosterone System inhibitors
  - Angiotensin Converting Enzyme (ACE) inhibitors (like ramipril)
  - Angiotensin II Receptor Blockers (ARBs)
  - Direct Renin Inhibitors
- Lipid-lowering agents
  - Statins
    - Atorvastatin
    - Rosuvastatin

    - Simvastatin
    - Other statins
  - Non-statins (like fibrates, binding resins and nicotinic acid)
- Diuretics
  - Thiazide diuretics
  - Non-thiazide diuretics
- Anti-diabetic medications
  - Insulin
  - Oral hypoglycemic agents
    - Thiazolidinediones
    - Metformin and other biguanides
    - Sulfonylureas
    - Alpha glucosidase inhibitors
    - DPP-4 inhibitors
    - Glinides
    - Other oral hypoglycemic agents
  - GLP-1 analogs
- Aldosterone antagonists
- Proton pump inhibitors
- Treatments for macular degeneration

Additionally, the time course of the total daily dose of concomitant statins will be reported at baseline and tracked over time. For this purpose doses of different statins will be equated according to Table 5-2. Mean statin dose, the number of changes in statin dose, and patients on each standardized dose level will be summarized over time and displayed graphically, where possible. Patients will be classified according to whether they receive no, low dose, medium dose or high dose statins at baseline and during the study. This will be done separately by time since index MI (including finer categorizations than $<$ versus $\geq$ 6 months post index-MI) and by region and/or country. If new statins become available or substantial new information regarding their lipid lowering effects becomes available, this table may have to be updated.

Table 5-1 Conversion table for statin doses

Low / Medium / High doses defined by Tom:		Low dose statin			Medium dose	High dose statin		
Standardized statin dose[1] [mg] (atorvastatin equivalent)	Scaling factor	2.5	5	10	20	40	80	160[2]
Atorvastatin (LIPITOR)	× 1			10	20	40	80	
Lovastatin (MEVACOR)	/ 4	10	20	40	80			
Pravastatin (PRAVACHOL)	/ 4	10	20	40	80			
Simvastatin (ZOCOR)	/ 2	5	10	20	40	80		
Fluvastatin (LESCOL)	/ 8	20	40	80				
Rosuvastatin (CRESTOR)	× 4				5	10	20	40
Pitavastatin / itavastatin (LIVALO)	× 20				1	2	4	
Ezetimibe 10 mg + Simvastatin (VYTORIN, INEGY)	× 2 standardized statin dose				10/10	10/20	10/40	10/80
Any other statin + ezetimibe or resin binders (e.g. colesevelam, cholestyramine, colestipol)	× 4 standardized statin dose							

[1] All other other drugs containing a statin should be reported for the statin dose only (including the following):
Statin + fenofibrate, + clopidogrel, + acetylsalicylic acid, + amlodipine, + ramipril

[2] Efficacy response curves flatten at the maximal equivalence of atorvastatin 160 mg or rosuvastatin 40 mg: further LDL lowering attempts with other lipid lowering drugs do not yield further LDL lowering. I.e. any calculated standardized statin dose > 160 mg will be considered as a standardized statin dose of 160 mg.

Furthermore, for the purpose of safety analyses, key drugs for the trial population affected by CYP450 with a narrow therapeutic index (e.g. warfarin and amiodarone) and vaccines (also by how long ago the vaccination was) will be identified.

6 Efficacy evaluation

The primary analysis and all analyses of secondary/exploratory variables will be conducted according to the intention-to-treat principle on the Full Analysis Set (FAS). Unless otherwise specified all time-to-event analyses will be based on events occurring during the double-blind phase (i.e. both from the double-blind treatment phase and the post-treatment phase). Unless otherwise specified "treatment groups" will refer to the four treatment groups canakinumab 300 mg, 150 mg, 50 mg or placebo. Comparing these separate active doses individually versus placebo will be the main method of analysis, but analyses of all canakinumab doses pooled versus placebo, as well as the active doses versus each other will also be conducted and dose response will be considered as described in section 6.5.

6.1 Variables

An overview of the primary, key secondary and other secondary variables as well as their components is given in Table 6.1. At the end of the study all endpoints will have been adjudicated by the Clinical Events Committee (CEC). The investigator reported events will only be considered as supportive. In order to assess the robustness of results at interim analyses the DMC will also be informed about events that have either been confirmed by adjudication, or reported by the investigator and not yet adjudicated. Events that have either been confirmed by the CEC or reported by the investigator but not yet been adjudicated will primarily be used for DMC activities to account for the time lag in adjudication.

Table 6-1 Primary, key secondary and secondary variables for CANTOS

Endpoint (variable is time to endpoint)	Adjudication committee (CEC) confirmed	Investigator reported	CEC confirmed or non-adjudicated investigator reported ("unrefuted")
Major adverse cardiovascular events (MACE)	Primary	Supportive	Primarily for DMC monitoring
CV death	Supportive	Supportive	Primarily for DMC monitoring
fatal or non-fatal Myocardial infarction	Supportive	Supportive	Primarily for DMC monitoring
fatal or non-fatal stroke	Supportive	Supportive	Primarily for DMC monitoring
MACE or hospitalization for unstable angina requiring revascularization	Key secondary	Supportive	Primarily for DMC monitoring
hospitalization for unstable angina requiring revascularization	Supportive	Supportive	Primarily for DMC monitoring
New onset of diabetes	Key secondary	Primarily for DMC monitoring	Primarily for DMC monitoring
All-cause mortality	Secondary	Primarily for DMC monitoring	Primarily for DMC monitoring
All-cause mortality or myocardial infarction or stroke	Secondary	Supportive	Primarily for DMC monitoring

6.1.1 Primary efficacy variable

The primary efficacy variable is the time to first occurrence of a major adverse cardiovascular event (MACE), which is a composite endpoint consisting of cardiovascular death, non-fatal MI, and stroke.

The primary clinical endpoint MACE is a well-established endpoint for CV trials. An external Clinical Events Committee (CEC) will review and adjudicate all clinical events that constitute MACE and the key components of secondary endpoints on a blinded basis.

The individual components of MACE will be also analyzed as part of the primary efficacy analysis.

- Cardiovascular death
- Myocardial infarction (fatal or non-fatal)
- Stroke (fatal or non-fatal)

The time-to-event is computed as the number of days from randomization to the onset of the primary endpoint event. In the case of patients dying due to a MI, the date of the MI and not the date of death is considered to be the date of the endpoint. Data on patients who do not

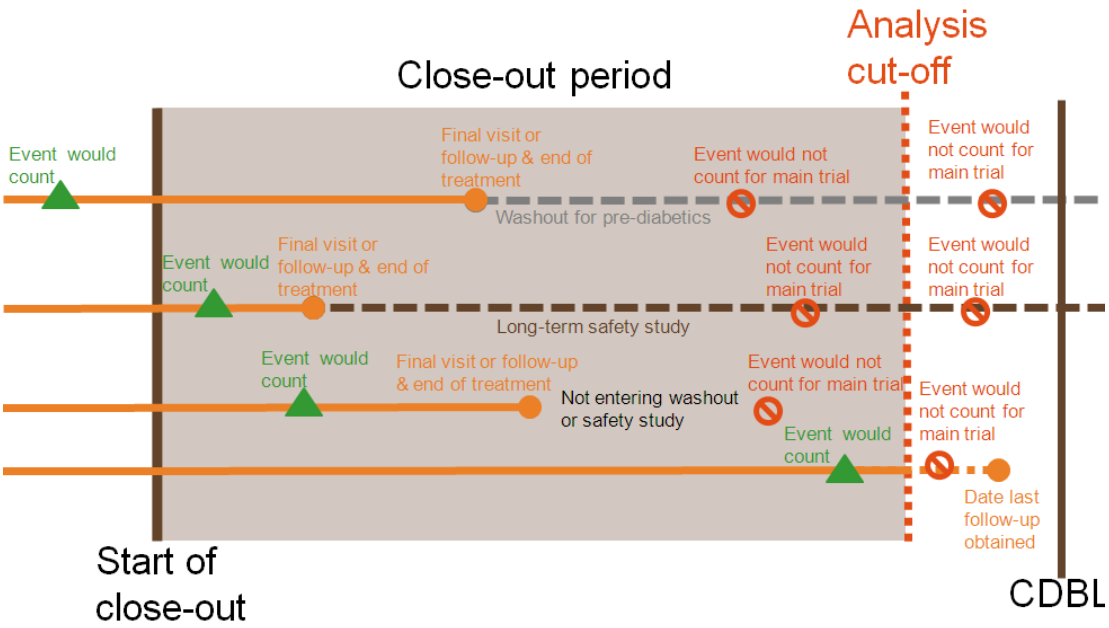
reach the primary endpoint by the study end date will be censored at the latest date they are known to be at risk.

Unless otherwise specified all time-to-event analyses will be based on events occurring during the double-blind phase (i.e. both the double-blind treatment phase and the post-treatment phase). This means that only events between a patient's randomization and the first of either

1. the patient's entry into the wash-out period (= end of study visit for the main study),
2. or the patient's entry into the long-term safety extension study (=end of study visit for the main study),
3. or for those patients proceeding to neither wash-out period nor safety extension the patient's end of study visit, but only if it occurred during the close-out period,
4. or otherwise the end of the close-out period (analysis cut-off)

will be counted in these analyses as shown in Figure 6-1.

Figure 6-1 Illustrative examples of events counting for the primary analysis



Note: for patients entering the washout for pre-diabetics or the long-term safety study, events would be appropriately reported as part of the respective reports. Events occurring after study completion in subjects not entering either washout or long-term safety study may still be subject to SAE reporting requirements and will be reported accordingly as per Novartis processes, if applicable.

Reporting of type of first endpoint

The type of first endpoint will be identified as

- the first primary endpoint component (CV death incl. fatal MI or fatal stroke, non-fatal MI and non-fatal stroke) that occurs after randomization
- if more than one endpoint occurs on the same day, then for the purpose of reporting the type of the first endpoint a fatal event will be reported by preference (i.e. CV death in

preference to a fatal-MI or fatal-stroke and these in turn in preference to a non-fatal MI or non-fatal stroke)

- should more than one endpoint fulfill the criteria above, then all of these will be reported (e.g. in case of both a non-fatal MI and non-fatal stroke on the same day "non-fatal MI and stroke" will be reported).

Note that the above only concerns the reporting of the type of the first endpoint. In the majority of tables the components of the primary endpoint will be shown separately and a patient may contribute to the numerator for no, one, two or all three components of the primary endpoint.

6.1.2 Key secondary efficacy variables

The following key secondary variables will be used in the analyses:

- Time to the first occurrence of an adjudication committee confirmed composite cardiovascular endpoint consisting of the components of the primary endpoint and hospitalization for unstable angina requiring unplanned revascularization
- Time to adjudication committee confirmed new onset of type 2 diabetes among those with pre-diabetes at randomization (i.e. excluding those that are normoglycemic at baseline)

6.1.3 Other secondary efficacy variables

The following other secondary efficacy variables will be used in analyses:

- Time to first event of MI, stroke, and all-cause mortality composite
- Time to all-cause mortality

Although all-cause mortality is considered a very important secondary endpoint due to its importance as both an efficacy and safety outcome, it is not part of the pre-specified testing procedure for primary and key secondary endpoints, because given the expected number of deaths in the trial it would not have been possible to adequately power the key secondary mortality endpoint.

6.2 Summarizing results across centers, countries and regions

As the target number of patients with a primary endpoint is not much larger than the number of centers, time-to-event analyses will be conducted on the pooled data from all centers without taking the center into account. However, the consistency of results by region will be explored.

6.3 Statistical hypothesis, model, and method of analysis

The primary analysis and all analyses of secondary/exploratory variables unless otherwise stated will use the Full Analysis Set (FAS), which reflects the intention-to-treat principle.

The familywise type I error rate for this trial will be controlled at the one-sided 2.5% level. One-sided testing at the 2.5% level constitutes an equivalent level of evidence as two-sided testing at the 5% level. Two sided p-values will also be provided.

6.3.1 Primary variable

The primary statistical null hypotheses are

- H_{11}: The hazard rate of first adjudication committee confirmed MACE in the canakinumab 300 mg dose group is greater than or equal to the hazard rate of the placebo group
- H_{21}: The hazard rate of first adjudication committee confirmed MACE in the canakinumab 150 mg dose group is greater than or equal to the hazard rate of the placebo group
- H_{31}: The hazard rate of first adjudication committee confirmed MACE in the canakinumab 50 mg dose group is greater than or equal to the hazard rate of the placebo group.

Each null hypothesis is tested against the one-sided alternative that the hazard rate is smaller for the respective active dose group than for the placebo group.

These hypotheses will be tested by comparing each dose to placebo with a log-rank test stratified by time since index MI (30 days to < 6 months and ≥ 6 months) and trial part using Peto's exact method (Peto 1972) for handling ties on the full analysis set (FAS) according to the intent-to-treat principle. The stratification according to trial part entails some statistical inefficiency compared to a trial that would have had 4 treatment groups from the start, especially for the 50 mg dose, because comparisons against the placebo group in trial part 1 are only indirect via the comparisons versus other doses in trial part 2. However, this approach ensures that no biases arise e.g. due to differences over time between the two trial parts in the recruited patient population or background medical care. While investigators are not blinded to the assignment of patients to randomization plan A or B, this is not believed to introduce any biases with respect to the assessment of the primary endpoint and the standard or care provided to patients, because patients have an equal chance of being on an active treatment group under either randomization plan. Thus, it was not considered necessary to also stratify the analysis in this respect, but a sensitivity analysis will be conducted. A sensitivity analysis with respect to the consistency of treatment effects in the two parts of the trial will also be performed.

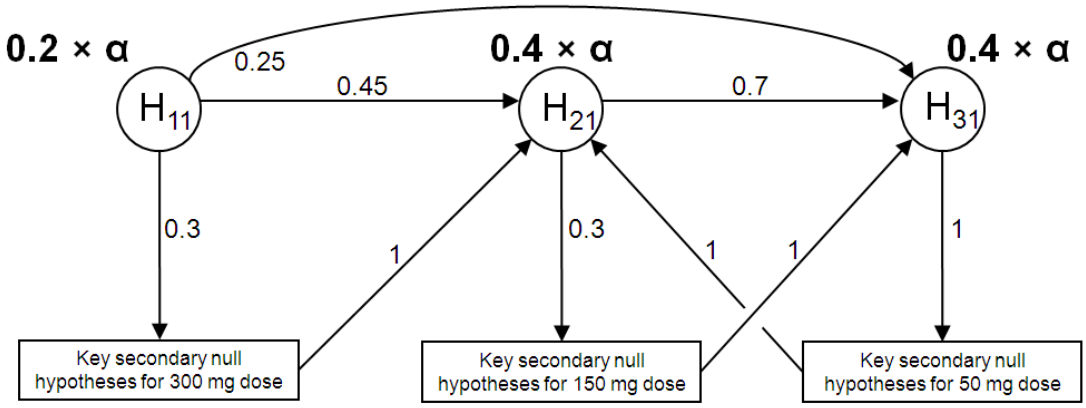
Note that no assumption of proportional hazards is necessary to test whether there is a higher probability of MACE in canakinumab than on placebo, because the employed stratified log-rank tests are valid even without proportional hazards. This assumption is only necessary to calculate estimated hazard ratios with confidence intervals for the effect of treatment (Bland and Altman 2004).

The family-wise error rate will be controlled at the two interim analyses and the final analysis using the closed testing procedure shown in Figure 6-3 based on the graphical method of Bretz et al. (Bretz, et al 2009); however, in intersection null hypotheses involving the primary null hypotheses for the 300 mg, 150 mg or 50 mg doses these primary null hypotheses will be tested using a weighted version of Dunnett's test (Dunnett 1955). Specifically this means that for any intersection hypothesis from the full closure that contains at least two of H_{11}, H_{21} and H_{31}, a weighted Dunnett test amongst the primary null hypotheses is performed with the overall significance level for that test and the weighting chosen according to the weights assigned to these null hypotheses by the update algorithm of the graphical method. The nominal adjusted significance levels based on the weighted Dunnett test are always slightly larger than the corresponding Bonferroni levels would be. For example the mvtnorm package in R (Genz and Bretz 2009) calculates the nominal Dunnett significance levels at the final

analysis for the 300 mg, 150 mg and 50 mg doses versus placebo adjusting for the interim analysis in the test of the global null hypothesis to be 0.5500504%, 1.1001008% and 1.1001008%, respectively, as compared to Bonferroni levels of 0.49%, 0.98% and 0.98%. If other non-primary null hypotheses in such an intersection hypothesis have non-zero weight on the basis of Figure 6-3, the intersection null hypothesis will be rejected if either (a) these other null hypotheses can be rejected at a Bonferroni significance level based on that weight or (b) the primary null hypotheses can be rejected based on the weighted Dunnett test.

To illustrate the link between trial objectives and the close testing procedure, it may be helpful to consider what the procedure might have looked like, if the Dunnett test had not been used. This is shown in Figure 6-2. As discussed in detail below, introducing a Dunnett test required modifications with several additional vertices to ensure consonance (see Figure 6-3).

Figure 6-2 Possible closed testing procedure if Dunnett test had not been used



All other intersection hypotheses are tested with a weighted Bonferroni test. Protection of the family–wise error rate at level alpha is still guaranteed when the transition weights on the directed edges are chosen as in Figure 6-3 (see comment below) and all the tests on secondary variables are performed at the level resulting from the graphical procedure. The consonance of the test procedure (Brannath and Bretz 2010) has also been ensured as described below.

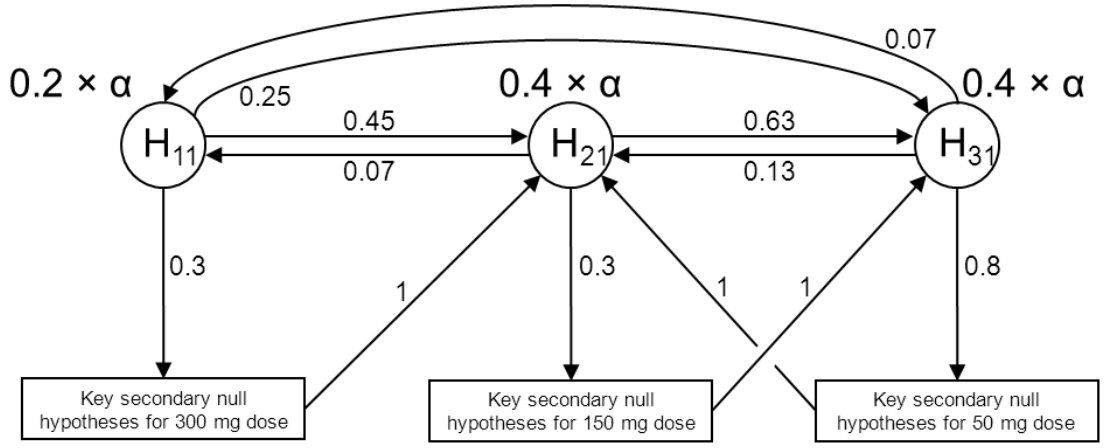
The testing procedure in Figure 6-3 initially splits the entire available significance level (at the final analysis 2.45%) between the three primary null hypotheses relating to the three doses (at the final analysis 20% of 2.45% = 0.49% for the primary null hypothesis of the 300 mg dose, 40% of 2.45% = 0.98% for that of the 150 mg dose and 40% of 2.45% = 0.98% for that of the 50 mg dose). These weights were chosen by balancing the prior expectations about the efficacy dose response relationship versus the potential for a better risk benefit ratio with lower doses. In particular, one aim was to ensure that there would be at least 80% power for the 50 mg dose to become significant assuming a 20% relative risk reduction for all doses. In the process of ensuring this, the weight for the 300 mg dose was reduced more than that of the 150 mg, because a higher dose is only of interest if it demonstrates a better efficacy than lower doses. This means that when the other doses are not effective the 300 mg dose would only become significant with a relative risk reduction that is at least in the region of 17.5%, while for the 150 mg dose this would already be the case with relative risk reductions below

16%. However, this was considered acceptable in order to ensure the desired operating characteristics for the 150 mg and 50 mg dose.

Key secondary variables for a dose are tested using a weighted Bonferroni-Holm procedure (Holm 1979) only after successful rejection of the primary null hypothesis for that dose. In that case, a higher fraction of the local significance level that is passed from the primary null hypothesis for a dose to the key secondary endpoint for the same dose is assigned to the secondary CV composite endpoint (90%) than to the new onset of diabetes endpoint (10%). The details for the key secondary endpoints are more fully illustrated in Figure 6-4 in section 6.3.2, which discusses the key secondary efficacy variables.

Note that if the primary endpoint for the 300 mg dose (null hypothesis H_{11}) is rejected 45% of the local significance level assigned to that null hypothesis is shifted to the primary endpoint for the 150 mg dose (null hypothesis H_{21}) and 25% to the primary endpoint for the 50 mg dose (null hypothesis H_{31}). This reflects the possibility that lower doses could potentially have a better safety profile than higher doses; hence, it would be desirable to demonstrate the efficacy of lower doses even after demonstrating the efficacy of a higher dose. In contrast, the main reason why some of the local significance level assigned to lower doses is shifted to higher doses is to preserve the consonance of the test procedure; i.e. to avoid a situation in which e.g. the primary null hypothesis for the 300 mg would be rejected by the weighted Dunnett test, but could not be rejected by the chosen closed testing procedure due to insufficient alpha being assigned to some intersection null hypotheses.

Figure 6-3 Closed testing procedure for primary and key secondary endpoints



When the primary null hypothesis for a dose is rejected, some of the local significance level assigned to that primary null hypothesis is passed to the key secondary null hypotheses for the same dose. These are then tested using a weighted Bonferroni-Holm procedure at the available local significance level with weights of 90% for the key secondary CV composite and 10% for the key secondary new onset of diabetes endpoint. Only if both key secondary null hypotheses for a dose are rejected, will any of the local significance level assigned to these null hypotheses be passed on to null hypotheses for other doses. See Figure 6-4 for a version of the graph showing full details of the Bonferroni-Holm procedure for the key secondary endpoints.

Two efficacy interim analyses, at which the trial could be stopped for demonstrated efficacy, or one or both active arms could be stopped for futility, will be performed respectively after 50% and 75% of the target number of 1,400 patients have experienced a primary endpoint. Futility criteria and the criteria other than purely formal statistical significance required for

stopping the trial for demonstrated efficacy will be specified in the Data Monitoring Committee charter.

A fixed Bonferroni split of the one sided significance level will be used to account for the two efficacy interim analyses and the final analysis, with a significance level of 0.01% for the first and 0.04% for the second efficacy interim analysis. I.e. the closed testing procedure will be performed with an one-sided significance level of 0.01% at the first efficacy interim analysis, with an one-sided significance level of 0.04% at the second efficacy interim analysis and with an one-sided significance level of 2.45% at the final analysis. In this fashion the familywise type I error rate will be controlled at the overall (one-sided) significance level $\alpha = 2.5\%$.

The appropriate nominal weighted Dunnett significance levels will be calculated e.g. using the mvtnorm R package (Genz and Bretz 2009). For the example of the global null hypothesis this can be done using R code (or corresponding SAS code) similar to the following

```
library(mvtnorm)
alpha <- 0.0245 # level at which Dunnett test is performed
rho <- 0.5 # assumed correlation of test statistics
corr <- (1-rho)*diag(3)+rho # correlation matrix
weight <- c(0.2,0.4,0.4) # weights for hypotheses in Dunnett test
alphaw <- alpha*weight
MVN <- function(alpha1, w, corr, alpha){
      x<-qnorm(1-alpha1*w)
      return(1-pmvnorm(upper=x,corr=corr) - alpha)
      }
opt3 <- uniroot(MVN, lower = alpha, upper = 2*alpha, w=weight,
corr=corr, alpha=alpha, tol=1E-12)
critwDun <- qnorm(1-opt3$root*weight)
nominal <- opt3$root*weight
```

The hazard ratios and their associated confidence intervals will be estimated by means of a (Cox 1972) proportional-hazards model stratified by time since index MI (< 6 months, ≥ 6 months) and by trial part (trial part 1, trial part 2) using treatment (canakinumab doses and placebo) as a factor in the model using (Peto 1972) exact method for handling ties. This will be done using SAS code similar to the following (or equivalent code in another programming language such as R):

```
proc phreg data=dataset;
  class treatment(ref="Placebo") <time since index MI> <trial part>;
  model time*event(0) = treatment / ties=exact risklimits;
  strata <time since MI > <trial part>;
run;
```

Should one of the three active arms be stopped due to safety reasons or futility, then thereafter the pre-specified testing procedure will be performed for the other arms treating all null hypotheses for the stopped arm as non-rejected. In such a case where one active arm is

stopped, then additionally the target number of patients with a MACE that is still to be collected has to be adjusted. It will be reduced by 20.5%. The size of this reduction is based on the proportion of events assumed to be available for the non-stopped comparison during sample size calculations. Under the main scenario for sample size calculation, all active arms have a 20% relative hazard reduction and the placebo group has 1.5 times as many patients as the active treatment groups; thus, under this scenario the expected proportion of events on any active arm is $0.8/(1.5\times1+0.8+0.8+0.8)\approx0.205$. While it is not clear, whether there is any adjustment rule for determining the target number of patients with an event after stopping one trial arm that can be absolutely guaranteed to have no effect on the type I error rate, it is expected that the conservativeness of the testing strategy in this case will outweigh any such small effects.

Supportive, sensitivity and subgroup analyses for the primary endpoint

The components of the composite primary efficacy endpoint (CV death, fatal or non-fatal MI, fatal or non-fatal stroke) will also be analyzed individually in order to evaluate their contributions to the overall treatment effect. No adjustment for multiplicity is foreseen for this purpose.

The three pooled canakinumab doses will be compared to placebo on the primary composite endpoint and its components, because in case of similar efficacy on all three doses this would be the most powerful test of the scientific hypothesis addressed by this trial. Additionally, when all three doses have similar efficacy, such a pooled analysis approach may provide the most precise information on the effects in subgroups.

Dose response will be evaluated using the methods discussed in section 6.5. Additionally, comparisons between the canakinumab doses based on the primary model will also be reported.

Kaplan-Meier type analyses will be presented as described in section 6.4 overall and by trial part to summarize the time to first event in the composite endpoint, by presenting the time-dependent cumulative frequency and percentage of patients who reach the primary composite endpoint by treatment group. Additionally, log time by treatment interaction will be evaluated to identify violations in the proportional hazards assumption, which might indicate a time-varying treatment effect. An Anderson-Darling type test based on a score process (cumulative sum of the Schoenfeld residuals) as recommended by Kvaløy and Neef (Kvaløy and Neef 2004) will be performed. For each trial arm within each trial part $-\log(S(time))$ vs. time and $\log(-\log(S(time)))$ vs. $\log(time)$ will be plotted.

The primary variable will also be analyzed on the PPS. Additionally, in an on-treatment analysis on the FAS, patients will be considered censored at the latest 28 days after the end of the double-blind treatment phase, which corresponds to up to 119 days after the last study drug injection based on the long elimination half-life of the drug. 91 days constitute a bit over 3 half-lives and 28 days add an additional half-life. In the on-treatment analysis patients will stay in the risk set until this point unless otherwise censored before and will not leave and re-enter the risk set due to treatment interruptions. Besides adjudicated endpoints investigator reported outcomes will also be analyzed on the FAS.

A covariate-adjusted Cox-regression model will be fitted with pre-specified baseline covariates, namely, linear age, sex, race/ethnicity, linear BMI, smoking status, region as defined in section 2.2, linear baseline log hsCRP, type of qualifying MI (STEMI/NSTEMI/Unknown), glycemic status, duration of diabetes for diabetic patients, hypertension, linear baseline systolic blood pressure, linear and quadratic baseline diastolic blood pressure, history of heart failure, dyslipidemia, linear baseline LDL-C, linear baseline HDL-C, linear baseline triglycerides, linear number of prior MIs, prior PCI, prior TIA/stroke, linear eGFR, no/low or medium dose/high dose statin use at baseline as defined in section 5, baseline aspirin therapy, baseline P2Y12 therapy, RAAS inhibitor use, beta blocker use, to account for other factors that might affect prognosis.

Furthermore, the pre-specified subgroup analyses will be conducted for the subgroups listed in section 2.2. Results will be presented graphically as forest plots. The objective of the subgroup analyses is to evaluate the consistency of treatment effects across a wide variety of patient groups. For this purpose the availability of data from three different doses should be helpful, because most subgroup effects would be affect all doses to some extent, which provides an additional way of identifying spurious findings that occurred by chance. Additional subgroup analyses will be considered and potentially pre-specified prior to unblinding of trial database for final analysis. It is clear that due to the number of subgroups a substantial number of totally spurious numerical imbalances in treatment effects between subgroups has to be expected – including some with an interaction p-value ≤ 0.05 and/or with apparently no or reversed effects.

Additionally, the post-baseline subgroups of response in hsCRP response and target hsCRP levels achieved will be explored. The appropriate target levels and response definitions will be defined based on an evaluation of the baseline data once recruitment is completed.

To assess whether pooling randomization plan A and B in trial part 2 is appropriate, the placebo groups in randomization plans A and B will be compared against each other, the 150 mg groups in randomization plan A and B will be compared and the 150 mg versus placebo contrasts will be compared qualitatively between randomization plan A and B.

As a further sensitivity analysis in this respect, randomization plan will be used as an additional stratification factor in the primary model. This analysis will use SAS code similar to the following (where randomization plan would be a 3 level stratification factor with 1 level for trial part 1 and two further levels for each randomization plan in trial part 2) or equivalent code in another programming language such as R:

```
proc phreg data=dataset;
  class treatment(ref="Placebo") <time since index MI>
      <randomization plan>;
  model time*event(0) = treatment treatment*<randomization plan>
      / ties=exact risklimits;
  strata <time since index MI> <randomization plan>;
  hazardratio treatment / diff=ref cl=both;
run;
```

A sensitivity analysis with respect to the consistency of treatment effects in the two parts of the trial will also be performed. This analysis will use SAS code similar to the following or equivalent code in another programming language such as R:

```
proc phreg data=dataset;
  class treatment(ref="Placebo") <time since index MI> <trial part>;
  model time*event(0) = treatment treatment*<trial part>
      / ties=exact risklimits;
  strata <time since index MI> <trial part>;
  hazardratio treatment / diff=ref cl=both;
run;
```

Calculation of multiplicity adjusted one- and two-sided p-values

Multiplicity adjusted p-values will be calculated for each null hypothesis as the smallest significance level at which one can reject that null hypothesis using the testing procedure shown in Figure 6-3 while also taking into account the interim analyses. For this purpose the algorithm described by Bretz et al. (2009) will be applied to the unadjusted one-sided p-values and the resultant p-values (adjusted only for the multiple endpoints and doses) will be adjusted for the interim analyses by scaling them by a factor of 250 (=0.025/0.0001) at the first efficacy interim analysis, 62.5 (=0.025/0.0004) at the second efficacy interim analysis and 0.025/0.0245 (≈1.02) at the final analysis. Because a weighted Dunnett test will be used for any intersection hypothesis from the full closure that contains at least two of H_{11}, H_{21} or H_{31}, the algorithm of Bretz et al. (2009) needs to be extended. For this purpose the weights w_{11}, w_{21} and w_{31} used as part of that algorithm would be defined as the respective Dunnett level divided by the overall significance level at the respective analysis.

For example, for the global null hypothesis instead of w_{11}=0.2, w_{21}=0.4 and w_{31}=0.4 as for a Bonferroni test based procedure – for which $w_{11} + w_{21} + w_{31} \leq 1$ would always hold – instead $w_{11} + w_{21} + w_{31} > 1$ would hold in this case. For example, using the nominal Dunnett significance levels for 300 mg, 150 mg and 50 mg doses at the final analysis calculated using the mvtnorm package in R as described earlier in section 6.3.1, one obtains w_{11} = 0.5500504% / 2.45% ≈ 0.2245103, w_{21} = 1.1001008% / 2.45% ≈ 0.4490207 and w_{31} = 1.1001008% / 2.45% ≈ 0.4490207.

In case health authorities, journals or the data monitoring committee require two-sided p-values, these will be provided in a manner that firstly ensures that the test decision on the rejection of the primary and key secondary null hypotheses remains unchanged and that secondly uses in principle the same testing procedure for evaluating the potential superiority of placebo over each dose of the test drug.

On this basis, the same test procedure as shown in Figure 6-3 will also be conducted in a one-sided fashion on the 2.5% significance level to test for the superiority of placebo over each canakinumab dose arm. The multiplicity adjusted two-sided p-values for each canakinumab dose arm will then be calculated as the minimum out of

- 2 × the multiplicity adjusted one-sided p-value for the superiority of that canakinumab dose arm over placebo,

- 2 × the corresponding multiplicity adjusted one-sided p-value for the superiority of placebo over that canakinumab dose arm versus
- and 1.

Exploration of dose response relationship and the effects of induction dosing in terms of cardiovascular endpoints

The method described in section 6.5 will be applied to assess dose response on cardiovascular endpoints over the whole duration of the trial.

It will be explored whether the early high induction dose regimen in 300 mg canakinumab arm has an impact on early (within 90 days of randomization) primary and secondary clinical cardiovascular events when compared to the placebo arm and to the 150 mg and 50 mg canakinumab arms, which have no early high induction dose regimen. For this purpose the primary endpoint and its components will be assessed over 90 days post-randomization with patients at risk but event free at the end of day 90 being considered censored after day 90. Similarly later timer periods (e.g. 90 days to 6 months, 6 months to 1 year, 1 year to 2 years etc.) will be analyzed separately, even though the risk sets at the start of such periods will not be fully randomized to treatments any longer. A separation between the 300 mg dose from the other doses over this time period in combination with no such (or an attenuated) separation over subsequent time periods might be indicative of a positive effect of induction dosing. How 50 mg and 150 mg doses lie relative to 300 mg and placebo over time will provide some ability to assess whether any effect observed in this respect is simply an attenuation of treatment effects over time. However, this trial is likely not powered to detect small to moderate effects of induction dosing. Event rates over the time periods from randomization to day 15, from day 15 to day 90 and subsequent time periods will also be considered, but the number of events between randomization and day 15 may limit the utility of such analyses.

6.3.2 Key secondary efficacy variables

The following hypotheses will be tested with respect to the key secondary variables for the canakinumab 300 mg dose versus placebo

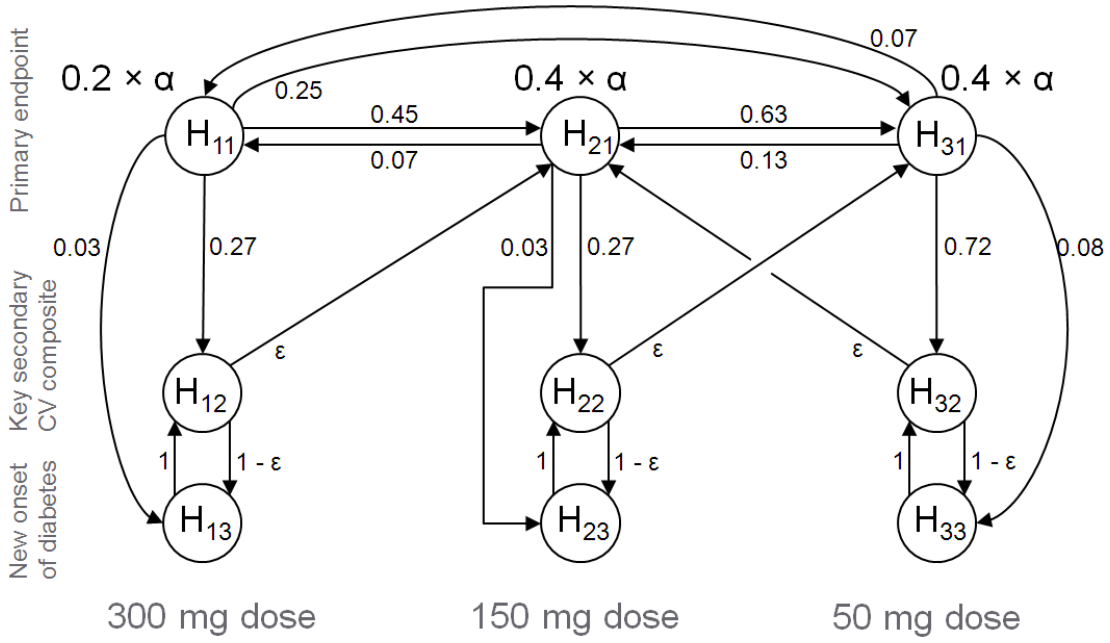
- H_{12}: The hazard rate of first adjudication committee confirmed secondary composite CV endpoint in the canakinumab 300 mg dose group is greater than or equal to the hazard rate of the placebo group
- H_{13}: The hazard rate of new onset of diabetes for pre-diabetic patients in the canakinumab 300 mg dose group is greater than or equal to the hazard rate of the placebo group

Each null hypothesis is tested against the one-sided alternative that the hazard rate is smaller for the canakinumab 300 mg dose group than in the placebo group. The corresponding hypotheses for the comparison of the canakinumab 150 mg dose versus placebo are H_{22} for the secondary composite CV endpoint and H_{23} for the new onset of diabetes endpoint. For the 50 mg dose they are H_{32} for the secondary composite CV endpoint and H_{33} for the new onset of diabetes endpoint.

All key secondary efficacy variables will be analyzed on the FAS with a log-rank test stratified by time since index MI and trial part. The hazard ratios will be estimated using a Cox regression model stratified by time since index MI and trial part. Kaplan-Meier plots

showing each treatment will be provided overall and by trial part as described in section 6.4. The multiplicity adjustment used to protect the familywise type I error rate is shown in Figure 6-3 and showing the full details of testing the key secondary endpoints in Figure 6-4. For each dose analyses of key secondary endpoints will be conducted even if the primary null hypothesis for the dose has not been rejected, but formally no rejection of the null hypotheses for the key secondary endpoints will be possible in that case.

Figure 6-4 Closed testing procedure with full details of testing of key secondary endpoints



This figure as compared to Figure 6-3 shows the full details of the Bonferroni-Holm procedure for the key secondary endpoints in a graphical form, but is otherwise identical in content.

Based on this testing procedure, once the primary null hypothesis for a dose has been rejected the key secondary endpoints for that dose are tested using a weighted Bonferroni-Holm test (Holm 1979) at the available local significance level for the key secondary endpoints for that dose. The weighting of this Bonferroni-Holm procedure will be 90% for the key secondary CV composite and 10% for the key secondary new onset of diabetes endpoint.

The secondary efficacy variable corresponding to new onset diabetes in patients with pre-diabetes at randomization will be the time from randomization to the first of repeated FPG > 126 mg/dL or the first of repeated HbA1c ≥ 6.5% or start of new anti-diabetic concomitant medication(s) for glucose lowering purpose. Due to the discrete nature of the visits when new onset of type 2 diabetes can be determined, events identified at the same visit time point as defined in section 2.3.6 for different patients will be considered as tied events and Peto's exact method for handling ties (Peto 1972) will be used. This assumes that for each of these patients new onset of diabetes occurred at some time point since the previous visit, but that due to the impossibility of continuous monitoring of the patients the true order in which each of them progressed to diabetes is unknown (Allison 1995, pp. 127 to 137). For this variable

patients without new onset of diabetes will be considered censored at the time of their last laboratory assessment. Patients not diagnosed at a regular visit or at the study completion visit will be assigned to one of the scheduled visits as per the algorithm in section 2.3.6.

Supportive and sensitivity analyses for key secondary endpoints

To support the analysis for the new onset of diabetes endpoint, the criteria defining new onset will be presented, the diagnostic values causing diagnosis summarized and sensitivity analyses conducted based on each criterion alone.

The three pooled canakinumab doses will be compared to placebo on the key secondary endpoints. Dose response will be evaluated using the methods discussed in section 6.5. Additionally, comparisons between the canakinumab doses will also be reported using the pre-specified log-rank test with hazard ratios reported based on Cox regression.

The key secondary cardiovascular endpoint will also be analyzed adjusting for the same covariates used for the covariate adjusted analysis of the primary variable.

The key secondary new onset of diabetes endpoint will also be analyzed adjusting for linear age, sex, race/ethnicity, region as defined in section 2.2, linear baseline FPG, linear baseline HbA1c, family history of diabetes, linear baseline log hsCRP, linear body mass index, smoking status, alcohol use (categories based on baseline distribution), linear baseline eGFR, linear baseline HDL, linear baseline triglycerides, linear baseline SBP/DBP, exercise (rarely/never, less than once a week, once a week, 2-3 times a week, 4-6 times a week, daily – combined into larger categories to ensure sufficient patients are in each category), baseline use of beta blockers and baseline use of diuretics.

The key secondary new onset of diabetes endpoint will also be supported by analyses using data from the study's washout period. As these analyses will only be conducted after the washout – i.e. after the main part of the trial has already been reported – and require extensive detailed pre-specification, these analyses are explained in Appendix 1 to this analysis plan.

6.3.3 Other secondary efficacy variables

As stated in section 6.1.3 all-cause mortality is considered a very important secondary endpoint due to its importance as both an efficacy and safety outcome, but it is not part of the pre-specified testing procedure for primary and key secondary endpoints, because given the expected number of deaths in the trial it would not have been possible to adequately power the key secondary mortality endpoint.

All-cause death and the composite of all-cause death, stroke or MI will be analyzed on the FAS with a log-rank test stratified by time since index MI and trial part. The hazard ratios will be estimated using a Cox regression model stratified by time since index MI and trial part. Kaplan-Meier plots showing each treatment will be provided both overall and by trial part. Patients who did not die will be considered censored at the last time they were reported to be alive.

These secondary endpoints will also be analyzed adjusting for the same covariates used for the covariate adjusted analysis of the primary variable.

The three pooled canakinumab doses will be compared to placebo on the other secondary endpoints. Dose response may be evaluated using the methods discussed in section 6.5 if needed. Additionally, comparisons between the canakinumab doses will also be reported.

6.3.4 Exploratory Efficacy variables

Exploratory time-to-event outcomes will be analyzed using Cox models including treatment with time since index MI and trial part as stratification variables, along with Kaplan-Meier analyses overall and by trial part. Exploratory continuous outcome variables (i.e. change from baseline of HbA1c, biomarkers, etc.) will be analyzed using both a repeated measures random effects analysis adjusted for baseline value, trial part, and time since index MI as a factor, as well as a descriptive analysis. For exploratory endpoints the three pooled canakinumab doses will also be compared to placebo.

Other cardiovascular disorders with a known inflammatory component

The following variables will be analyzed.

- Time to other cardiovascular disorders with a known inflammatory component:
  - Time to first deep vein thrombosis/pulmonary embolism
  - Time to first supraventricular tachycardia/atrial fibrillation
  - Time to first stent thrombosis (probable or definite)
  - Time to first hospitalization or prolongation of hospitalization for heart failure or cardiovascular death due to heart failure/cardiogenic shock, and the components of this composite:
    - Time to first hospitalization or prolongation of hospitalization for heart failure
    - Time to first cardiovascular death due to heart failure/cardiogenic shock
  - Time to first event of major coronary events composite: CHD death or MI, where CHD death is defined as a death due to myocardial infarction, congestive heart failure/cardiogenic shock, directly related to revascularization, due to arrhythmias, due to witnessed sudden death, unwitnessed sudden death seen within 24 hours, unwitnessed death, death due to unknown cause or due to other vascular causes identified as Ischemic Heart Disease (i.e. fulfilling the narrow “Ischaemic heart disease” SMQ)
  - Time to first event of total vascular events composite consisting of primary endpoint, hospitalization for unstable angina, or for any other non-coronary ischemic event (transient ischemic attack or limb ischemia), any revascularization procedure (coronary and non-coronary) and limb amputation
  - Time to first event of coronary revascularization procedures (PCI or CABG)
  - Time to first event of stroke by etiology

As the number of events for some of these events is expected to be limited, the three pooled canakinumab doses will be compared to placebo for these variables.

As long as sufficient events (e.g. >20 events per covariate) are available, the same covariates as for the primary endpoint will be used in covariate adjusted analyses. In addition, for stent

thrombosis history of previous stents (and type of stent) will be taken into account, as this substantially influences the risk of stent thrombosis; without a previous stent an event requiring stenting would first have to occur, before a stent thrombosis could occur.

For deep vein thrombosis/pulmonary embolism a more limited list of covariates will be used: linear age, sex, race/ethnicity, linear BMI, linear height, use of warfarin or other anticoagulants, history of deep vein thrombosis or pulmonary embolism.

Similarly, for the supraventricular tachycardia/atrial fibrillation endpoint a more limited list of covariates will be used: history of supraventricular tachycardia, history of atrial fibrillation and, use of medications such as digoxin, as well as age, sex and race/ethnicity.

While any reduction in the rate of occurrence for any of the exploratory endpoints under canakinumab treatment constitutes a benefit to patients, it is scientifically interesting whether any such treatment effect is secondary to the potential effect of canakinumab on the primary composite endpoint, since these endpoints are influenced by recurrent MI and, in some cases, stroke. To address this question, the first occurrence of that endpoint or the composite primary endpoint as competing risks will be analyzed using the approach of Lunn and McNeil (Lunn and McNeil 1995). For the example of hospitalization for heart failure this can be implemented using SAS code similar to the following

```
PROC PHREG;
  CLASS treatment(ref='Placebo') endpoint;
  MODEL <time to event or censoring>*<event indicator>(0)
      = treatment treatment*endpoint
      <further covariates> <further covariates >*endpoint;
  STRATA endpoint;
  HAZARDRATIO treatment / DIFF=REF;
RUN;
```

after augmenting the standard time-to-event dataset so that there are two records per patient. One record would be for hospitalization for heart failure and one record for the primary MACE endpoint. Both records would have the same time to event or censoring, namely, the minimum of time to event or censoring for MACE and time to event or censoring for hospitalization for heart failure. Only at most one of the two records would indicate an event, namely, the record for the endpoint, for which an event occurred first, if any. Furthermore, the time to the first occurrence of the composite of MACE and the additional endpoint of interest will be analyzed. For endpoints on which there is an impact of canakinumab these analyses will include estimation of cumulative incidence of this composite, as well as the number needed to treat, with estimation approaches based on those described for the primary endpoint.

Nephropathy and renal function

Time to nephropathy as assessed by urine albumin/creatinine ratio (≥ 30 mg/mmol) in patients with T2DM or pre-diabetes at baseline will be analyzed.

Only patients with a baseline urine albumin/creatinine ratio that is < 30 mg/mmol or missing will be included in this analysis. If nephropathy occurs, the time of the event will be the visit at which the laboratory sample was drawn. The analysis will be conducted in the same fashion as for new onset of diabetes with the same rules for censoring and tied event times.

Subgroup analyses based on the basis for diabetes diagnosis (FPG or HbA1c based versus only based on diabetes medication use) will be provided.

Additionally, the occurrence of nephropathy based on adverse event reporting, occurrence of the narrow SMQ Acute Renal Failure, doubling of serum creatinine, non-cardiovascular death due to renal failure and endstage renal disease (ESRD) defined as dialysis, renal transplant, or serum creatinine >530 µmol/L (6.0 mg/dL) will also be analyzed. An overall composite will also be provided. The laboratory data based outcomes will be analyzed in the same fashion as the new onset of diabetes endpoint based on the visit at which the lab sample was drawn, while other outcomes will be analyzed in the same way as the primary CV endpoint. As the laboratory based events are likely to be more frequent than the other components of the composite, the composite will be analyzed as if it were laboratory data based. The continuous log-transformed urine albumin creatinine ratio will be also analyzed as well as eGFR over time and abnormalities will be considered (see also section 7.4.8).

Predictive covariates will be taken into account in all models including baseline eGFR, baseline creatinine, baseline log urine albumin creatinine ratio, age, sex, race/ethnicity, baseline blood pressure, history of heart failure, antihypertensive drug use and baseline glycemic status.

Glycemic control among those with type 2 diabetes

The following two variables will be analyzed to compare glycemic control between the two canakinumab doses and placebo among those with type 2 diabetes at baseline. The following variables will be analyzed

- Time to failure of glycemic control defined as HbA1c ≥ 7.5% confirmed by a second HbA1c within 6 weeks in those patients that were diabetic at baseline with a baseline HbA1c < 7.0%
- Change from baseline in HbA1c overall, to the end of study and by visit in all patients that were diabetic at baseline; by visit analyses will use mixed model repeated measures analysis as described in section 7.2. to impute missing data assuming missing at random.

For the time to failure of glycemic control endpoint, the analysis will be conducted in the same fashion as for new onset of diabetes with the same rules for censoring and tied event times.

Both HbA1c analyses will use baseline value, and baseline BMI as continuous linear covariates, duration of diabetes and the use of diabetic medications at baseline (yes/no) as a factor in the analysis models. The effect of region will be explored in additional models.

Subgroup analyses based on the basis of diabetes diagnosis (FPG or HbA1c based versus only based on diabetes medication use) will be provided for the time to failure of glycemic control and change from baseline in HbA1c analyses.

Long-term glycemic control will also be looked at in terms of the change of slope in FPG/HbA1c increases over time using a mixed model approach.

Additionally the following will be analyzed:

- Change from baseline to each visit and to the end of study in FPG analyzed as for HbA1c
- Responder rates with respect to HbA1c ≤ 6.0%, 6.5% and 7.0% at the end of study (and by visit) including in the subsets of patients with HbA1c ≤ / > 8.0% at baseline
- Responder rates in terms of a reduction in HbA1c ≥ 0.5% at the end of study (and by visit)
- Responder rates in terms of FPG at end of study ≤ 6.1, 7.2, 7.8 or 10.0 mmol/L (≈ 110, 130, 140 or 180 mg/dL)

Change from baseline in FPG will be analyzed in an analogous fashion as HbA1c, except that baseline FPG is used in the model instead of HbA1c. Binary response variables will be analyzed using logistic regression models including the respective baseline value (HbA1c or FPG as appropriate), baseline BMI, use of diabetic medications at baseline, duration of diabetes, treatment and region. Response rates will be analyzed over the whole trial duration using a generalized linear model with a logit link. The generalized estimated equation method with an unstructured correlation matrix as the working correlation structure and the same model covariates will be used.

As potential sensitivity analyses on-treatment analyses will be conducted. As a further sensitivity analysis, data after the initiation of a new anti-diabetic drug will be considered censored/missing. For any continuous data analyses these data would be imputed when using a mixed model repeated measures analysis with a missing at random assumption. Subgroup analyses will be conducted based on age groups, gender, race, region, ethnicity, baseline HbA1c (where appropriate), linear BMI, and linear duration of diabetes.

Biomarkers of cardiovascular and diabetes risk

Change from baseline in biomarkers of cardiovascular and diabetes risk, including but not limited to inflammatory biomarkers, glycemic control markers, β-cell function markers, FPG and HbA1c, including achieved reductions from baseline in hsCRP and target hsCRP levels achieved (to be defined based on baseline characteristics once recruitment is completed)

will be analyzed. When analyzed as a continuous variable hsCRP will be log-transformed and results reported as geometric means and ratios of geometric means with adjustment for baseline values. Additional analyses will adjust for age, sex, race/ethnicity, region, education, exercise level, alcohol use, smoking history, BMI and hypertension.

Multiple occurrences of the primary composite MACE endpoint

The numbers and rates of individual components of MACE (allowing for multiple events per patient) will be analyzed on the FAS set and summarized by treatment group and trial part. For a single patient multiple MIs or strokes may be considered to have occurred. Fatal MIs or fatal strokes will only be counted as a separate event from the patient's death, if the death occurred more than 1 day (i.e. ≥ 2 days) after the MI or stroke. Rates will be compared between treatment groups based on Negative Binomial regression including terms for treatment, trial part, and log (time at risk) as offset variable. A 95% confidence interval will

be provided for the ratio (active dose group vs. control) of rates for each MACE component. The SAS procedure GENMOD, will be used to conduct the analysis.

Occurrence of diabetic complications

The occurrence of diabetic complications such as retinopathy, nephropathy, neuropathy, foot ulcers or dermopathy will be compared between treatment groups based on adverse event reporting (and in the case of nephropathy also in terms of laboratory data). The difference in the occurrence of such events or in nephropathy assessed by urine albumin/creatinine ratio could further support the benefit of patients indicated by improved glycemic control with canakinumab in diabetic patients or a lower incidence of new diabetes diagnoses with canakinumab in pre-diabetic patients. As this would rely on adverse event reporting as opposed to more systematic assessments and the timeframe of the trial may be too short to see an effect on such outcomes, it is possible that no difference will be seen in these events even if canakinumab were to prevent such events over a sufficiently long timeframe. For these reasons this assessment is considered a potentially supportive exploratory assessment.

Subgroup analyses based how diabetes was diagnosed at baseline will be provided.

As the number of events for some of these events is expected to be limited, the three pooled canakinumab doses will also be compared to placebo for these variables.

Macular degeneration

Whether patients had a history of or current macular degeneration at baseline will be identified via a suitable set of MedDRA terms applied to the reported medical history. These MedDRA terms will be pre-specified prior to clinical database lock.

In patients with age-related macular degeneration at baseline occurrence of worsening and/or need for treatment will be looked at in terms of incidence and also using time-to-event methods corresponding to the primary analysis model (both as a composite and looking at these two endpoints separately) including ones taking into account predictive covariates. Worsening will be defined as a post-baseline AE report of the MedDRA terms also used at baseline. Similarly, the same criteria will be applied to reasons for the use of concomitant medications or non-drug interventions to identify treatment for macular degeneration. However, adverse event reports may be the most important source of information, because a treatment due to a worsening of disease as opposed to the continuation of ongoing treatment may not be distinguishable.

In patients without age-related macular degeneration occurrence thereof (same criteria as for worsening above) and/or need for treatment (same criteria as above) will be summarized and analyzed using time-to-event methods including ones taking into account predictive covariates. Kaplan-Meier type analyses will also be presented in both patient groups. The same censoring date as for the primary MACE endpoint will be used and time to event will be defined as time from randomization to the AE or medication start date.

The baseline categorization and type of reported post-baseline events will both be summarized by MedDRA preferred terms, type of concomitant medications and reasons for their use by MedDRA preferred term for each medication.

The following potentially prognostic covariates will be taken into account in analyses of macular degeneration linear age, sex, race/ethnicity, smoking status, linear baseline log hsCRP, alcohol use, linear baseline BMI, linear baseline SBP/DBP.

6.3.5 Patient reported outcomes and health economic analyses

Exploratory efficacy patient reported outcome variables including those related to tiredness, physical function, performance function and health status, will be generated from the Modified Rankin Scale, MGSI-SF, SF-36, SIS-16, EQ-5D, Heath State Classification, and Visual Analogue Scale. These will be analyzed using a repeated measures analysis of covariance with baseline levels as a covariate and summarized descriptively.

Details of the MGSI-SF and SF-36 analyses, which are being assessed on a subset of patients in the US and predefined EU countries will be specified separately, prior to completion of the first Interim Analysis.

The MFSI-SF and SIS-16 analyses, part of the Stroke Functional Assessment Sub-study, will also be specified separately, prior to completion of the first Interim analysis.

The EQ-5D analyses, done on all patients enrolled, are specified below.

6.3.5.1 Health-related quality of life (EQ-5D)

EQ-5D index is a standardized measure of health status developed by the EuroQoL Group in order to provide a simple, generic measure of health for clinical and economic appraisal EuroQoL Group (2009). EQ-5D essentially consists of 2 pages:

- the EQ-5D descriptive system that compromises the dimensions mobility, self-care, usual activities, pain/discomfort and anxiety/depression, with each having 3 levels (no problems, some problems, severe problems), and
- the EQ visual analogue scale (EQ VAS)

Scoring

Descriptive System

The EQ-5D descriptive system includes codes that indicate the level of the perceived problem. This section of the EQ-5D should be scored as follows.

- Level 1 (no problem) is coded as a "1"
- Level 2 (some problem) is coded as a "2"
- Level 3 (severe problem) is coded as a "3"

Missing values should be left blank and coded as ",". Ambiguous values (e.g., two boxes are checked for a single dimension) should be treated as missing values and coded as missing.

Scoring the VAS

The EQ VAS should be scored as the number, between 0 and 100, where the response crosses the VAS. If the line does not cross the VAS, the response can still be scored by drawing a horizontal line from the end point of the response to the VAS. Missing values should be left

blank and coded as ".". Ambiguous values (e.g., the line crosses the VAS twice) should be treated as missing values.

Converting EQ-5D States to a Single Summary Index

EQ-5D health states, defined by the EQ-5D descriptive system, will be converted into a single summary index or utility weight by applying a formula that attaches a value weight to each level in each dimension. The index (utility weight) will then calculated by deducting the appropriate value weights from 1, the value for full health (i.e., state 11111). Since sets of value weights differ across cultures and countries, one country-specific set of value weights (eg: US) will be identified in the primary analysis. Sensitivity analyses using different sets of value weights will be conducted.

Data will be displayed graphically over time.

Planned reporting as part of Clinical Study Report

The EQ-5D descriptive system, EQ-5D VAS and EQ-5D index will be summarized descriptively by treatment group.

The EQ-5D VAS and EQ-5D index values will be compared between treatment groups. Statistical comparisons of treatment groups will be performed using analysis of variance with Fisher's least significant difference.

In addition, EQ-5D VAS (EQ-5D index similarly) will be compared between treatment groups and it will be analyzed using a random-coefficient selection model (Fairclough 2002) for supportive analysis. In a random-coefficient model the relationship between EQ-5D VAS (EQ-5D index) and time is investigated. It is also possible that this relationship varies between patients and this is done by simply modeling a separate regression of EQ-5D VAS (EQ-5D index) on time for each patient. In the most common applications a linear relationship is assumed between the outcome variable of interest and time (the approach can be expanded to polynomial or non-linear functions). In this simplified approach patient effects provide the intercept terms for each patient and a patient by time interaction the slopes.

In fitting linear random coefficient models the time, treatment and treatment by time interaction are fitted as fixed effects while patient and patient by time effects as random. Furthermore region (or country) is also fitted in the model as fixed effects. Baseline EQ-5D VAS (EQ-5D index) is considered in the model as the first repeated measurement at time zero.

The additional assumption made in the random coefficient mixed models is that the patient effect (intercepts) and patient by time effects (slopes) are correlated within each patient. Therefore, separate normal distributions are used for each random effect with means of both effects equal to zero and an unstructured variance structure (Brown and Prescott 2006).

It is of primary interest to test the difference of the slopes in the treatment groups. Estimates of the random coefficients are usually of no interest but they can be tested based on Kenward-Roger method. The denominator degrees of freedom will be calculated using the Kenward-Roger method (Kenward and Roger 1997) and an unstructured variance-covariance matrix will be used.

6.3.5.2 Health care resources utilization, defined as the components of the medical care used by patients in the trial

For endpoint related hospitalizations as well as other hospitalizations and data on reason for hospitalization, length of stay, and procedures for diagnostic and therapeutic purposes will be collected. Data on out of protocol physician visits and post-acute care, as well as concomitant medication will also be collected.

Number of hospital admissions for the whole trial

The number of hospital admissions (total and by unit) will be analyzed on the FAS and summarized by treatment group. Treatment groups will be compared based on Negative Binomial regression (Glynn and Buring 1996) with the number of hospital admissions as the dependent variable. The log of time on (prolonged) treatment in years will be used as the offset variable to obtain the point estimate as a rate (number of hospital admissions/number of years in study). The 95% confidence intervals will be provided for the rate ratios (X vs. Y) of hospital admissions. See section 7.2 for details.

Number of days in hospital for the whole trial

Number of days in hospital will also be analyzed on the FAS set and summarized by treatment group. The total number of days in hospital will be calculated as the sum of the days in hospital [including intensive care unit (ICU) days and critical care unit (CCU)] for each individual hospitalized event/admission. For descriptive purposes, the annualized days in hospital, taking into account all hospitalizations with admission date during the double-blind phase, will be calculated for each patient as the number of days of hospitalization divided by total duration of the double-blind phase, then multiplied by 365.25. As described above, the number of days in hospital as the dependent variable will be analyzed and adjusted for treatment duration (log of time on treatment in years will be used as the offset variable) using Negative Binomial regression. The number of days in ICU will also be summarized and analyzed similarly.

In addition to the inferential analysis, descriptive summaries will be presented for the total number of hospital admissions and number of days in hospital for each treatment group.

Sensitivity analysis for hospital admissions and days in hospital

A non-parametric approach will be implemented as a sensitivity analysis for the number of hospital admissions and days in hospital. Patients will be ranked according the following scheme:

1. Patients without hospitalizations will get the “best case” rank
2. For patients who were hospitalized, ranks will be assigned in ascending order of number of hospital admissions (or days in hospital) per patient year.
3. In a second analysis the impact of patient who died will be assessed. Patients who died will get a “worst case” rank with further ranking of the number of hospital admission (days in hospital per patient year as under 2) while the patient was still alive.

The null hypothesis will be tested by assigning ranks on the number of hospital admissions (days in hospital), that a patient had during double-blind phase and then testing the location shift of the medians across the treatment groups. Treatment groups will be compared using the Wilcoxon rank sum test. The significance level for testing treatment differences will be set at the 2-sided 5% level.

6.4 Kaplan-Meier type analyses and graphs

Because this trial has two consecutively recruited trial parts with different allocation ratios that may differ in important predictive covariates and since one treatment group is not even represented in trial part 1, simply pooling data across trial parts to produce an overall Kaplan-Meier graph would not be appropriate. For this reason an alternative approach for producing such a Kaplan-Meier type graph is described in section 6.4.1 below. Such graphs and within any trial part Kaplan-Meier plots will follow the general principles described in section 6.4.2.

Kaplan-Meier type analyses and plots will be provided (including by trial part) for the primary endpoint, key secondary endpoints, secondary endpoints and a selected subset of exploratory outcomes.

6.4.1 Overall Kaplan-Meier type graphs across trial parts

A Cox model stratified for treatment group (placebo, 50 mg, 150 mg or 300 mg) and time since index MI (30 days to < 6 months, ≥ 6 months), with trial part as a covariate will be used to obtain Breslow estimates (Breslow 1974) for the predicted survival curves for each combination of treatment group, time since index MI and trial part – including for the 50 mg group in trial part 1. These predicted survival curves will then be aggregated for an appropriate cohort of patients within each of the 4 treatment groups to obtain a single overall Kaplan-Meier type graph for the 4 treatment groups.

The use of a Cox model stratified for treatment group (placebo, 50 mg, 150 mg or 300 mg) – and also time since index MI (30 days to < 6 months, ≥ 6 months) – is a suggestion by Zhang et al. (Zhang et al. 2007) and Terry Therneau (personal communication, 2011). As pointed out by Zhang et al. such a model makes no assumption of proportional hazards between treatment groups or time since index MI groups. Thus, it is more appropriate for obtaining a graphical representation that allows an inspection of the relative effectiveness of treatment groups over time. Using trial part as a covariate and assuming the same proportional effect of trial part for the whole follow-up period for each of the 8 strata (treatment group / time since index MI) allows extrapolation of what a 50 mg group in trial part 1 would have been like, as suggested by Terry Therneau (personal communication, 2011). To assess the assumptions involved the predicted survival curves from this model for the placebo, 150 mg and 300 mg groups in each stratum and for the 50 mg group in all trial part 2 strata will be compared graphically to those from a model that treats trial part as an additional stratification variable. Should the assumption be strongly violated with respect to trial part having a constant effect over time, it would be an alternative to assume a trial part effect that is only proportional over specific time intervals (e.g. up to 90 days, day 91 to day 183, days 184 to 1 year, 1 year to 2 years, > 2 years).

The overall aggregated cohort survival estimate will be obtained from the estimates for each treatment group / time since index MI / trial part combination using the Hakulinen method

(Hakulinen 1982). Compared with the more simple Ederer method this is expected to more closely reflect what might have been obtained, if this study had been conducted with 4 treatment arms from the start. The reason is that the follow-up time after which administrative censoring at trial end will occur will differ – by design – between the trial parts (Thomsen et al. 1992) (Therneau and Grambsch 2000, pp. 261-287).

The cohort for which the cumulative failure rate is estimated using the Hakulinen method will be constructed so that within each trial part the distribution of time since index MI and distribution of maximal potential follow-up is the same for each treatment group. To achieve this within each trial part

1. All the patients in all treatment groups and time since index MI strata in that trial part are selected.
2. Their length of follow-up $\mathbf{F_i}$ and time since index MI information is retained.
3. These patients are assumed to be the (identical) hypothetical recruited cohorts for each of the four treatment groups.

Note that the length of follow-up $\mathbf{F_i}$ is taken to be

- for those patients that were censored: the time from randomization to the maximum actual follow-up for CV events (not just for the first event)
- for patients that had a non-fatal version of the endpoint of interest (e.g. non-fatal MI in case of analyzing the primary MACE endpoint) the same approach as for those patients that were censored will be used
- for patients that had a fatal version of the endpoint of interest (e.g. fatal MI in case of analyzing the primary MACE endpoint) the maximum potential follow-up will be used, i.e. the time from randomization to the maximal potential follow-up date, defined to be the analysis cut-off date (see Section 2.3.7).

For each patient **i** let $\mathbf{S_i(t)}$ be the estimated survival curve based on that patient's treatment group, time since index MI and trial part. If patients are ordered from shortest to longest possible follow-up time $\mathbf{F_{(1)}, F_{(2)}, \ldots, F_{(K)}}$, then the Hakulinen estimate (Hakulinen 1982) for the cumulative survival function $\mathbf{S(t)}$ is calculated recursively for any $\mathbf{F(k) < t \leq F(k+1)}$ as

$$\mathbf{S(t) = S(F_{(k)}) \times [\ \Sigma_{i=1,\ldots,n}\ S_i(t) \times 1\{\ F_i > t\ \}\ ] / [\ \Sigma_{j=1,\ldots,n}\ S_j(F_{(k)}) \times 1\{\ F_j > F_{(k)}\ \}\ ]}$$

as described by Thomsen et al. (Thomsen et al. 1992), Nielsen (Nielsen 1997) and Therneau and Grambsch (Therneau and Grambsch 2000, pp. 261-287).

Note that valid confidence intervals cannot be obtained for these estimates in a straightforward fashion, because of the artificially inflated "apparent sample size" resulting from the way in which the algorithm above ensures balanced time since index MI/trial part across treatment groups and censoring patterns. If pointwise confidence intervals are required (e.g. primary and secondary endpoints) one could create e.g. B=2,000 bootstrap samples, repeat the whole process above (starting from fitting the Cox model) for each bootstrap sample and then obtain interval percentile (or BCa) Bootstrap confidence intervals as described by Efron and Tibshirani (Efron and Tibshirani 1993, pp. 170-176 and pp. 184-188) e.g. for times t=1 year, 2 years, 3 years and 4 years. algorithm might be applied.

6.4.2 Kaplan-Meier graphs for each trial part and general principles

The approach for Kaplan-Meier graphs closely follows the recommendations by Pocock et al. (2002).

Cumulative event rate estimates (1 – estimated survivor function) in % versus time of follow-up in years will be shown based on Kaplan-Meier estimates. Compared to showing the survivor function this maximizes detail without needing a break in the scale.

While "technically, any survival plot can be extended right through to the longest follow-up time" as Pocock et al. point out "this extension is not good statistical practice, since for any such plot the eye is drawn to the right (i.e. where the plot finishes), which is where there is least information and greatest uncertainty". Kaplan-Meier curves will therefore only drawn up to the time at which the total population at risk for the event in question has decreased to 10% of the size of the analysis set. This matches the recommendation by Pocock et al. who wrote that they "[..] recommend that survival plots be halted once the proportion of patients free of an event, but still in follow-up, becomes unduly small. […] What constitutes "unduly small" is open to debate and depends on the context. It will often be reasonable to curtail the plot when only around 10–20% are still in follow-up." As CANTOS is a large outcome trial the lower end of this range (10%) will be used.

For the kind of Kaplan-Meier type graphs described in section 6.4.1 above, this will be taken to mean that the graph will be truncated at the length of follow-up achieved by 10% of patients across all trial arms and trial parts. This means that the graph for the 50 mg dose will be continued somewhat past the point up to which 10% of 50 mg patients were followed up.

The number of patients at risk in each group will be displayed below the x-axis at year=0, 1, 2, 3… and each subsequent year of follow-up to provide information on the extent of follow-up. Pointwise 95% confidence intervals at each full year will be shown. In line with the recommendations by Pocock et al. this provides some measure of statistical uncertainty and ensures that any visual signs of treatment differences do not look more convincing than they really are. Results of inferential statistics (e.g. primary model-based hazard ratios, 95% confidence intervals and p-value for primary endpoint) will also be shown on the figure. Kaplan-Meier tabulations will show number at risk, number failed, cumulative number failed, cumulative number censored, Kaplan-Meier estimates of failure rate with pointwise 95% confidence intervals. Similar tabulations will be provided by time interval also including the estimated hazard at interval midpoint.

It is recognized that just as discussed by Pocock et al. caution is needed in interpreting the shape of survival plots in particular due to the lack of any pre-specified hypothesis about its shape and the lack of statistical power to explore subtleties of treatment difference other than the overall comparison.

6.4.3 Calculation of number needed to treat

The number needed to treat (to benefit) will be calculated using the method of Altman and Andersen (Altman and Andersen 1999) for each dose for different durations of treatment as

$$\mathbf{NNT\ (t) = 1 \,/\, [\ S_{placebo}(t)^{\text{hazard ratio for dose versus placebo}} - S_{placebo}(t)\ ]}$$

using S(t) calculated as described in section 6.4.1. It will be extrapolated as described by Altman and Andersen to the 5 year timepoint from the timepoint of follow-up achieved by 10% of patients across all trial arms and trial parts $T_{10\%}$ under the assumption of approximately constant event rates and benefit as

NNT (5 years) = ($T_{10\%}$ / 5 years) × NNT ($T_{10\%}$).

3 year and 1 year NNTs will be calculated and it is expected that this can be done without such an extrapolation unless the study is stopped an interim analysis. Confidence intervals with appropriate coverage probabilities will be calculated using Bootstrap methods.

6.5 Methodology for dose response evaluation

If the pre-specified closed testing procedure described in section 6.3.1 and section 6.3.2 confirms efficacy for any canakinumab dose versus placebo for either the primary or the key secondary endpoints, then a dose response has obviously already been established even if the methods described in this section do not suggest a significant dose response. On the other hand, if the pre-specified closed testing procedure has not led to significance for any canakinumab dose versus placebo for either the primary or the key secondary endpoints, then any dose signal detected would in the strict regulatory confirmatory sense only be of an exploratory nature. For that reason, the main purpose of the analyses described below for the primary and key secondary endpoints is to characterize the nature of any already confirmed dose response. On the other hand, if the method for adjusting for multiplicity in safety analyses (see in section 7.1) is based on frequentist methods, then the methodology described below could be used as part of that assessment of a drug effect and of dose response.

Different types of variables will lead to different types of analyses results that will be used in dose response evaluation, namely:

- estimates of the group means for each treatment group from an analysis of covariance for continuous variables (means on the log-scale for log-transformed continuous variables),
- for survival variables the linear predictor function for each treatment group from a parametric piecewise exponential model stratified in the same way as the primary analysis evaluated at the overall (i.e. across all treatment groups) median follow-up time (Note: the planned test for dose response requires estimators for each treatment group – including placebo. Therefore unlike for other efficacy analyses a parametric model will be employed, which is expected to provide the needed flexibility to reflect the likely non-constant hazard function.), and
- for repeatedly occurring events the linear predictor function for each treatment group from a negative binomial model.

These estimators will be assumed to have an asymptotic multivariate normal distribution. With this asymptotic normality assumption contrast tests with the flat dose response taken as the null hypothesis will be performed, each of which is by construction the most powerful contrast test to detect each of the shapes shown in figure 6.4. Using the maximum of the test statistics from all contrast tests as the test statistics with the critical value calculated so that

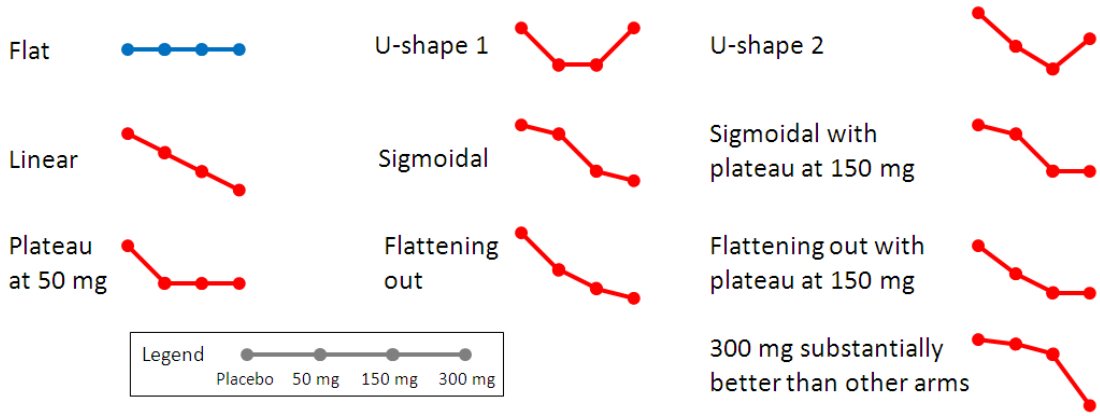
P{ Z_{max} > critical value | flat dose response } <= 0.05

as described by Stewart and Ruberg (Stewart and Ruberg 2000). On this basis a multiplicity adjusted p-value adjusted for the multiple doses and candidate dose response shapes (but not

adjusted for the number of outcome variables, yet) will also be calculated. If the method for adjusting for multiplicity in safety analyses (see in section 7.1) is based on frequentist p-value based methods, then this p-value could be used for safety outcomes.

In an explorative way the dose response shape will be described on the following basis: The diagnostic property of maximum tests will be employed, which Cox (Cox 1977) described for situations in which "(i) the component statistics assess departures of qualitatively different kinds; (ii) so far as is feasible failure of the null hypothesis in one respect should have relatively little effect on the meaningfulness of and the distribution of the statistics for the other aspects." As he points out when critical values are correctly calculated as above, then the resulting procedure has useful diagnostic properties for the nature of the departures from the null hypothesis. However, not all of the dose response patterns below constitute departures from the null hypotheses of qualitatively completely different kinds, because several of the contrasts shown in Figure 6.4 are strongly correlated to each other (for example the flattening out shape and the flattening out shape with a plateau at 150mg or the linear shape and the sigmoidal shape are rather similar). Only looking at the maximum of the statistics is therefore problematic. For that reason the bootstrap probability that a certain contrast out of those shown in Figure 6.4 has the largest contrast test statistic will additionally be calculated using numerical integration to give some indication as to how consistent the various dose response shapes are with the data. While the contrasts can be seen as a measure of how well the group means correlate with each of the candidate shapes, these bootstrap probabilities will provide an assessment of the uncertainty involved in the ranking of different shapes. This will also be taken into account when describing the results. As a sensitivity check for the numerical integration actual bootstrapping may be considered e.g. for the primary endpoint.

Figure 6-5 Candidate dose response patterns



7 Safety evaluation

Safety will be evaluated based on the safety set (SAF). The assessment of safety will be based primarily on the assessment of potential and identified risks defined in the safety profiling plan (SPP)/risk management plan (RMP), the frequency of adverse events, laboratory

abnormalities, and serious adverse events suspected by the investigators to be related to study treatments. Other safety data (like vital signs, ECG) will be summarized as appropriate.

Safety data will not be naïvely pooled across trial parts, but rather displayed separately for each trial part or in an appropriately combined fashion (see also section 2.4).

The primary key set of safety analyses will be based on looking at events and variables recorded while patients were still on investigational drug (i.e. data will be considered censored at the latest one quarter year + 28 days = 119 days after the last study injection). Selected safety information will also be provided including data after the end of treatment and for selected safety topics the primary focus will in fact be on this analysis (e.g. for malignancies). Especially initially, this approach will also be taken for data monitoring purposes, because of the potentially unclean status of the data, which may make it difficult to determine whether adverse events occurred on treatment.

Since the study is intended to be the only pivotal trial in the regulatory submission, selected key safety analyses including disposition, demographics, exposure, adverse events, serious adverse events, adverse events by narrow SMQ, serious adverse events by narrow SMQ, key outputs for adverse events of special interest, deaths, laboratory abnormalities and laboraty values over time will be repeated for those groups specified in table 2.3-2.

Selected safety analyses will also be shown by time period (prior to visit 2.5, from visit 2.5 to ≤90 days post-randomization, > 90 to ≤ 183 days post-randomization, > 183 to ≤ 365 days post-randomization and > 365 days post-randomization) due to the two different dosing regimens in the two active dose arms and to evaluate any changes in safety during more short-term and longer term treatment.

7.1 Safety assessment approach accounting for multiplicity

The most appropriate method for handling the multiplicity issues arising in the quantification of identified risks, evaluation of potential risks and search for additional unknown risks is still being considered. In particular, it is being evaluated how to compare canakinumab doses to placebo beyond descriptive statistics at the time of the study report using the safety database accrued during the double blind treatment period of CANTOS. While type I errors due to multiplicity are a concern on such a large safety database, type II errors are also an issue and an appropriate balance needs to be found. However, a structured statistical approach will help elucidate the strength of evidence and interpret putative statistically significant findings. For this reason methods that on the one hand are less conservative than controlling the familywise type I error rate, while still providing a quantifiable level of protection against false positive findings, are currently being evaluated. Options for example include approaches that control the false discovery rate or Bayesian hierarchical models – with possibly separate handling of potential and non-pre-specified risks. The process of evaluating different methods to better understand their operating characteristics is still ongoing.

7.2 Statistical models used in multiple safety contexts

Safety data will be summarized across the two trial parts and the two randomization plans in trial part 2, both of which might influence safety reporting as described in section 2.4.

For this purpose hazard ratios versus placebo will be estimated for binary safety outcomes (e.g. at least one occurrence of adverse events) using Cox regression stratified for time since index MI and trial part/randomization plan as for the primary endpoint. Time to event methods were chosen instead of relative risk regression or logistic regression, because in either case differential follow-up would have to be taken into account and time constant hazards may not be a reasonable assumption. This can be implemented using SAS code similar to the following:

```
proc phreg data=dataset;
  class treatment(ref="Placebo") <time since index MI>
      <trial part & randomization plan>;
  model time*event(0) = treatment / ties=exact risklimits;
  strata <time since MI > <trial part & randomization plan>;
run;
```

Trial part/randomization plan by treatment interactions will be investigated. For selected events, additional potentially predictive baseline covariates will be added to the model, namely age, sex, race, region and other event specific variables. As summary statistics patients with an event per 100 patient years of follow-up (defined as follow-up to first event or censoring) will be reported. If required, dose response can be evaluated using the methods described in section 6.5, potentially using a Weibull model as the behaviour of hazards over time are less clear than with the primary endpoint. Alternatively, if suitable software such as SAS version 9.22 or higher becomes available an order restriction within the Cox regression setting could be applied. These approaches are expected to be more powerful than a simple 3 degrees of freedom test for the effect of trial arm, although that test or a simple test of trend may be an easily implementable option for interim monitoring. In case too few events are available to ensure the normality assumptions described in section 6.5 are met or in case there are zero cells on some treatment groups, the above model cannot be used to assess whether there is a (safety) dose response signal. An appopriate cut-off still needs to be evaluated, but could e.g. be based on cell counts smaller than a certain number. In such cases the data could instead be considered as a 2 (trial parts) x 3 or 4 (treatment groups) x 2 (event yes/no) contingency tables ignoring the length of follow-up. Order restrictions with respect to the doses may be used for the purpose of analyses. Appropriate cut-offs, methods for this purpose and whether it is meaningful to statistically analyze such rare events still needs to be evaluated.

Rates of multiple occurrences of safety events will be compared between treatment groups for selected safety events of special interest, where such an analysis is of interest. A Negative Binomial regression including terms for treatment, trial part/randomization plan, and log (time at risk) as offset variable will be used. This model was chosen, because the number of recurrent events in a population will follow a negative binomial distribution if there is a distribution of different individual Poisson event rates in the population that follows a gamma distribution (Glynn et al. 1993) (Glynn and Buring 1996). While the population distribution may not exactly follow a gamma distribution, the maximum likelihood estimation of the additional dispersion parameter compared to the Poisson distribution from the data allows the negative binomial model approximate the data in this respect and to capture the extent of unexplained heterogeneity in the population. The logarithm of the time at risk is used as an

offset (i.e. as a covariate with coefficient 1), because a log link function is used in order to effectively analyze the rate of events per time unit. The model will be implemented using SAS code similar to the following or equivalent code in another programming language such as R:

```
PROC GENMOD DATA=events;
  CLASS treatment(ref='Placebo') <trial part & randomization plan>;
  MODEL <number of events> = treatment
      <trial part & randomization plan> / OFFSET=<log time at risk>
      DIST=NB LINK=LOG LRCI;
RUN;
```

As matching summary statistics, events per 100 patient years of follow-up will be reported. For selected events, additional potentially predictive covariates will be added to the model, namely at least age, sex, race and region. When selecting repeated events it has to be ensured that a single adverse event case report form entry is only counted once (e.g. by ensuring only one record per adverse event sequence number is counted), as analysis dataset may contain multiple records for one CRF report to allow identification via e.g. different SMQs.

When such a model is used for specific adverse events of interest and a sufficient number of events to make this display useful is available, these data will also be displayed graphically as events per unit time of follow-up for different time intervals (e.g. first 6 months, 6 months – 1 year, 1 year to 2 years … or smaller time intervals as appropriate) using meaningful categories of time to show time patterns of event occurrence and potential changes in treatment effect over time. Measures of uncertainty will be provided, as well as information on the extent of overdispersion / population heterogeneity.

Changes from baseline in continuous safety parameters will be plotted over time based on both trial parts with missing data imputed assuming missingness at random using a model repeated measures mixed model implemented with SAS code similar to the following or equivalent code in another programming language such as R:

```
proc mixed data=dataset;
  class subject visit treatment <trial part>
      <time since index MI>;
  model <change from baseline> = treatment visit treatment*visit
      baseline baseline*visit <trial part> <trial part>*visit
      <time since index MI> <time since index MI>*visit
      / s ddfm=kr;
  repeated visit / subject = subject type = un;
run;
```

with appropriately transformed values. Comparisons at each visit will be conducted in a corresponding fashion using analysis of covariance. Additional analyses will add potentially predictive covariates, namely age, sex, race/ethnicity, region education, exercise level, alcohol use, smoking history, BMI and hypertension to the model. The following variables will be

analyzed on the log-scales and results will be back-transformed to report geometric means and ratios of geometric means versus placebo:

- Urine albumin/creatinine ratio, urine albumin, urine creatinine
- ALT (SGPT), AST (SGOT), total bilirubin, direct bilirubin, alkaline phosphatase
- Triglycerides, HDL, IDL, VLDL
- hsCRP

All other safety variables will be analyzed without any transformation based on the arithmetic mean and differences in arithmetic means versus placebo.

Panel plots of the results of these analyses showing means/geometric means or differences in means/ratios of geometric means over time will be made available as in-text figures for the clinical study report. 95% pointwise confidence intervals will be provided to allow judgment on the variability in the underlying data, but due to the obvious multiplicity issues consideration of these confidence intervals or p-values from the model described above cannot form the basis of any formal inference.

7.3 Other safety evaluation

7.3.1 Adverse Events

Adverse events between informed consent and randomization

Adverse events between informed consent and randomization will be summarized by primary system organ class and preferred term for all randomized patients (as opposed to the safety set). This summary will include events that would qualify as trial endpoints if they occurred after randomization, but which are to be reported as AEs prior to randomization.

Serious adverse events occurring after informed consent will be reported for all screened patients, as well as separately for all randomized patients and for screen failures.

Treatment emergent adverse events (AEs) excluding trial endpoints

The incidence of treatment emergent AEs (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) excluding trial endpoints will be summarized by primary system organ class (SOC), preferred term and also by severity and relationship to study treatment. If warranted, time to event analysis methods will be used. Standardized MedDRA Queries (SMQs) will also be employed. The MedDRA version used for reporting the study will be clearly identified.

Any adverse events reported by the investigator prior to clinical database lock will be included in AE analyses irrespective of how long after last study drug intake or after the last study visit occurred. Adverse events occurring after a patient's final visit in CANTOS will be reported as part of the main CANTOS trial, as long as they started prior to the patient's entry into the washout or long term safety extension study. Adverse events occurring after entry into the washout will be reported as part of the washout, as long as they started prior to the

patient's entry into the long term safety extension study. Adverse events occurring after the patient's entry into the long term safety extension study, will be reported as part of that study.

If a patient reported more than one AE with the same preferred term, the AE with the greatest severity will be presented. If a patient reported more than one AE within the same primary system organ class, the patient will be counted only once with the greatest severity at the system organ class level, where applicable.

The number and percentage of patients reporting any AE during the double-blind phase of the study will be summarized by primary system organ class, preferred term and treatment and also by SMQ and treatment. The most common adverse events reported (reported by ≥ 1 % of patients in any group for each preferred term or ≥ 1 % in any group for each SMQ table will be presented in descending frequency starting from the most common event.

Separate summaries will be provided for AEs suspected by the investigator to be related to study drug, deaths, SAEs, other significant AEs leading to discontinuation, and adverse events leading to dose adjustment.

Events reported on endpoint pages

The following events reported on the trial endpoint pages will be summarized by treatment group for safety purposes, because they are as per the study protocol not reported as adverse events (further sub-categorizations may be added as needed):

- All-cause death
  - Non-cardiovascular death
    - Non-cardiovascular death due to accident/trauma
    - Non-cardiovascular death due to respiratory failure
    - Non-cardiovascular death due to infection/sepsis
    - Non-cardiovascular death due to malignancy
    - Non-cardiovascular death due to suicide
    - Non-cardiovascular death due to renal failure
    - Non-cardiovascular death due to liver failure
    - Non-cardiovascular death due to other non-vascular reason
  - Cardiovascular death
    - Coronary Heart Disease death
      - Cardiovascular death due to myocardial infarction
      - Cardiovascular death due to congestive heart failure/cardiogenic shock
      - Cardiovascular death directly related to revascularization
      - Cardiovascular death due to arrhythmias
      - Cardiovascular death due to witnessed sudden death
      - Cardiovascular death due to unwitnessed sudden death seen within 24 hours
      - Cardiovascular death (unwitnessed death)

        - Cardiovascular death (death due to unknown cause)
        - Cardiovascular death due to other vascular causes identified as Ischemic Heart Disease (i.e. fulfilling narrow "Ischaemic heart disease" SMQ)
    - Cardiovascular death due to other vascular causes not identified as Ischemic Heart Disease (i.e. not fulfilling narrow "Ischaemic heart disease" SMQ)
    - Cardiovascular death due to atherosclerotic non-coronary vascular disease
    - Cardiovascular death due to pulmonary embolism
    - Cardiovascular death due to stroke
        - Cardiovascular death due to non-hemorrhagic stroke
        - Cardiovascular death due to intracranial hemorrhage
- Stroke or TIA
    - Stroke
        - Non-hemorrhagic cerebral infarction
        - Non-hemorrhagic infarction with hemorrhagic conversion
        - Primary hemorrhagic intracerebral stroke
        - Stroke of uncertain type
    - Transient Ischemic Attack requiring/not requiring hospitalization
- Coronary vessels with >50% stenosis
    - Coronary vessels >50% stenosis: Left Main
    - Coronary vessels >50% stenosis: LAD
    - Coronary vessels >50% stenosis: LCX
    - Coronary vessels >50% stenosis: RCA
    - Coronary vessels >50% stenosis: Bypass Graft
- Myocardial infarction (with 12 sub-classifications as below)
    - Spontaneous myocardial infarction with/without new ST segment elevation with/without new Q waves identified
    - PCI-related myocardial infarction with/without new ST segment elevation with/without new Q waves identified
    - CABG-related myocardial infarction with/without new ST segment elevation with/without new Q waves identified
- Unstable Angina (with 4 sub-classifications as below)
    - Unstable angina requiring/not requiring unplanned revascularization and requiring/not requiring hospitalization
- Coronary revascularization (with 4 sub-classifications as below)
    - Urgent/Elective percutaneous coronary intervention without stenting/using drug eluding stent/bare metal stent/unknown type of stent
    - Urgent/Elective coronary artery bypass graft (1 bypass graft/>=2 bypass grafts)
- Non-coronary revascularization (with 21 sub-classifications as below)

  - Stenting/Surgical revascularization/Other revascularization of carotid artery/aorta/iliac artery/femoral artery/popliteal artery/renal artery/other artery
- Stent thrombosis in a previously stented segment
  - Stent thrombosis in a segment previously stented with a drug eluding stent
  - Stent thrombosis in a segment previously stented with a bare metal stent
  - Stent thrombosis in a segment previously stented with an unknown type of stent
- Hospitalization or prolongation of hospitalization for heart failure
  - Hospitalization or prolongation of hospitalization for heart failure with elevated BNP
  - Hospitalization or prolongation of hospitalization for heart failure with elevated NT-proBNP
  - Hospitalization or prolongation of hospitalization for heart failure with elevated BNP and NT-proBNP
  - Hospitalization or prolongation of hospitalization for heart failure without elevated BNP or NT-proBNP
- Critical limb ischemia (with 16 sub-classifications as below)
  - Critical limb ischemia requiring hospitalization
    - Critical limb ischemia in left lower extremity/left upper extremity/right lower extremity/right upper extremity requiring revascularization/not requiring revascularization and requiring hospitalization
  - Critical limb ischemia not requiring hospitalization
    - Critical limb ischemia in left lower extremity/left upper extremity/right lower extremity/right upper extremity requiring revascularization/not requiring revascularization and not requiring hospitalization
- Limb amputation due to vascular cause (with 10 sub-classifications as below)
  - Amputation of right lower extremity/right above knee amputation/…/left upper extremity
- Deep vein thrombosis (with 14 sub-classifications as below)
  - Deep vein thrombosis in left leg (proximal with calf/proximal without calf/calf only)/right leg (proximal with calf/proximal without calf/calf only)/other limb confirmed by diagnostic study/not confirmed by diagnostic study
- Pulmonary Embolism
  - Pulmonary embolism in left/right lung confirmed/not confirmed by at least one diagnostic study
- Supraventricular tachycardia/Atrial Fibrillation
  - Supraventricular tachycardia
  - Atrial fibrillation
  - Atrial flutter
  - Other arrhythmia
- New onset diabetes

- New onset diabetes based on start of new diabetes medication
- New onset diabetes based on laboratory criteria
  - New onset diabetes based on HbA1c only
  - New onset diabetes based on FPG only
  - New onset diabetes based on HbA1c and FPG

7.3.2 Laboratory data

Laboratory values that the laboratory reports to be below or above the limit of quantification will be imputed as 0.5 × and 1.5 × the respective limit of quantification. Should there be a substantial proportion of values below the lower limit of quantification and/or above the upper limit of quantification for an important laboratory parameter, the summary statistics (mean, standard deviation) will also be calculated as the maximum likelihood estimates using a parametric model for data that can be right censored and left censored at the upper and lower limit of quantification, respectively, using the following methods

- Arithmetic mean and SD are calculated using PROC LIFEREG assuming a normal distribution
- Geometric mean and CV%(geometric mean) are calculated using PROC LIFEREG assuming a log-normal distribution and back-transformed
- Empirical median will not be calculated in the case of censoring. Empirical minimum will not be calculated if there are values < lower limit of quantification, similarly the empirical maximum if there are values > upper limit of quantification.
- Quartiles from the parametric distribution can also be calculated upon request when Q1, median or Q3 does not lie between the lower and upper limits of quantification.

The summary of laboratory evaluations will be presented for three groups of laboratory tests (Hematology, Serum chemistry and Urinalysis).

Descriptive summary statistics (mean, median, standard deviation, Min and Max) for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by laboratory test and treatment group. Change from baseline will only be summarized for patients with both baseline and post baseline values and will be calculated as:

change from baseline = post baseline values – baseline value

In addition, shift tables will be provided for all parameters except for creatinine clearance in order to compare a patient's baseline laboratory evaluation relative to the visit observed value. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, or high for each visit value relative to whether or not the baseline value was normal, low, or high. These summaries will be presented by laboratory test and treatment group.

The frequency and percentage of patients with clinically notable laboratory results after baseline will be tabulated. Clinically notable laboratory results, for those parameters where ranges are available, are given in Table 7-1 below and are based on the FDA Division of Neuropharmacology guidelines. Only patients with laboratory results within the normal reference range from the central laboratory at baseline will be included in the tabulations.

Table 7-1 Clinical notable criteria for selected laboratory tests

Laboratory parameter (unit)	Lower bound of clinically notable range	Upper bound of clinically notable range
Hematology		
Hematocrit (%)	30	60
Hemoglobin (g/L)	100	200
Platelet count (x 10^9/L)	100	600
RBC (x 10^{12}/L)	3.3	6.8
WBC (x10^9/L)	3.0	15.0
Basophils (%)	-	6
Eosinophils (%)	-	10
Lymphocytes (%)	10	60
Monocytes (%)	-	20
Absolute neutrophils (x 10^9/L)	1	12
Chemistry		
Albumin (g/L)	25	60
Alkaline Phosphatase (U/L)	-	280
BUN (mmol/L)	0.7	14.3
Calcium (mmol/L)	1.87	2.89
Chloride (mmol/L)	85	119
Creatinine (mcmol/L)	18	221
LDH (U/L)	0	500
Potassium (mmol/L)	3	6
AST (U/L)	-	100
ALT (U/L)	-	110
Total Bilirubin (mcmol/L)	-	43
Total Protein (g/L)	40	95
Uric Acid (mcmol/L)	89	595
BUN/Serum Urea (mmol/L)	0.7	14.3
Sodium (mmol/L)	125	154

7.3.3 Vital signs

Descriptive summary statistics (mean, median, standard deviation, Min, Max) for the change from baseline to each post baseline visit will be presented. These descriptive summaries will be presented by vital sign and treatment group. Change from baseline will only be summarized for patients with both baseline and post-baseline values and will be calculated as:

change from baseline = post-baseline value – baseline value

The frequency and percentage of patients with clinically notable vital signs changes from baseline will be tabulated. Clinically notable vital sign results are provided in Table 7-2 below. Pulse pressure will be derived as systolic – diastolic blood pressure and reported.

Table 7-2 Clinically notable changes in vital signs

Vital Sign (unit)	Clinically notable criteria
Weight (kg)	decrease > 7% from Baseline
	increase > 7% from Baseline
Systolic blood pressure (mmHg)	<90 and decrease from baseline of >20
	>180 and increase from baseline of >20
Diastolic blood pressure (mmHg)	<50 and decrease from baseline of >15
	>105 and increase from baseline of >15
Pulse (bpm)	<50 and decrease from baseline of > 15
	>120 and increase from baseline of >15

7.3.4 Electrocardiogram (ECG)

In the CANTOS trial, baseline and yearly thereafter ECGs will be taken; ECG results will be centrally read for changes including QTc changes and silent MIs for clinical CAD endpoints.

The following quantitative variables will be summarized at each visit using standard summary statistics: ventricular rate (heart rate), RR interval, PR interval, QRS duration, QT interval, and corrected QT interval (QTcF/QTcB). The difference between treatment groups in observed values and changes from baseline with associated 95% confidence interval will be provided for each of these criteria. QT data will be analyzed for both the Fridericia (primary) and Bazzett's (secondary) corrections.

Additionally, the number and proportion of patients with

- QT > 550 ms
- QT > 500 ms
- QTc > 500 ms
- QTc > 480 ms
- QTc > 450 ms
- QTc changes from baseline > 30 ms
- QTc changes from baseline > 60 ms
- Sinus pause > 3 s
- PR > 250 s

will be computed and compared between treatment groups using Cox regression as described in section 7.2. The difference between treatment groups and associated 95% confidence interval will be provided for each of these criteria. QT data will be analyzed for both the Fridericia (primary) and Bazzett's (secondary) corrections.

In addition, shift tables comparing baseline ECG results (normal, abnormal, not available, total) with the maximum on-study result (normal, abnormal, not available, total) will be provided for each variable.

Newly occurring or worsening abnormalities will also be summarized by treatment group. Results in elderly patients, by gender, in patients with congestive heart failure, elevated

baseline QT/QTc intervals (for QT/QTc analyses) and baseline HR <55 bpm will also be considered as necessary.

7.4 AE and non-AE safety analyses of special interest

This section outlines the currently planned analyses based on the current safety profiling plan. The safety profiling plan is an evolving document outlining the clinical safety plan at any stage of the clinical development of a compound. Thus, due to the length of the trial the analyses based on potential and identified risks may have to be updated according to new information while the trial is ongoing.

In general, analyses for adverse events of special interest based on a list of search criteria to be provided by the Novartis Brand Safety Leader, which will be stored in the Novartis Clinical REsearch Documentation and Information system (CREDI). Both broad and narrow MedDRA searches will be used, when available. For each DMC any analyses to be included in DMC reports will be communicated to the academic independent statistician. Number of affected patients and percentage will be provided by treatment arm. Risk ratio and 95% confidence interval will be provided for each dose versus placebo. If unbalances occur, time to first occurrence and number of occurrences will be evaluated, if appropriate and not already pre-specified. Dependent on the risk medical history or baseline characteristics may have to be considered further beyond what is prespecified below.

When some set of MedDRA terms was combined into a search, then what preferred terms where identified by the search will be summarized by preferred term. Additionally, such summaries will be provided by high level term including secondary paths with the understanding that the same even might then be counted under multiple high level terms.

Multiplicity in safety outcomes will in general be described as described in section 7.1. For sufficiently frequent safety events and continuous safety data, dose response can be evaluated as described in section 7.1, sections 6.5 and section 7.2, respectively.

The frequencies of adjudicated serious infections, and malignancies will be reported.

Whenever a sufficient number of events is available age, sex, race/ethnicity and region will be added to models for adverse events of special interest. Interactions with treatment for these and other potentially predictive covariates will be explored whenever possible.

Subgroups for which these adverse events of special interest will be evaluated include those evaluated for efficacy, as well as those specified for safety analyses.

7.4.1 Infections / opportunistic infections

Infections as adjudicated will be summarized based on the adjudicated information including whether the infection was classified as opportunistic, whether the infection was typical or atypical based on the patient's medical history, response to standard antibiotic therapy, whether it was a chronic recurrent infection/exacerbation of a previous infection and the presence of risk factors for infections. The analyses below will be conducted for both adjudicated and investigator reported infections.

Additionally, all infections will be identified using a list of search criteria to be provided by the Novartis Brand Safety Leader, which will be stored in CREDI. The occurrence of such

events will be reported by MedDRA preferred term, MedDRA high level term and MedDRA high level group term.

These will be classified by severity, seriousness, whether hospitalization was required, whether intravenous antibiotics were required, whether infection AEs/SAEs were suspected to be related to study drug by the investigator and whether study drug was discontinued due to infections. Non-cardiovascular death due to infection/sepsis will also be analyzed. Time to first infection will also be analyzed both in a stratified Cox regression model, as well as using Kaplan-Meier type analyses.

Since infections are expected to be sufficiently frequent in a long-term study to allow the use of multiple covariates, age, sex, race/ethnicity, and region will be added to models.

Rates of infections including repeated infections will also be looked at graphically and using negative binomial regression as described in section 7.2 and will be summarized including graphs of infections in different time periods. The following time intervals will be used 1-3 months, 3-6 months, 6-9 months, 9-12 months, 12-18 months, 18-24 months, 24-30 months and so on in 6 month intervals for as long as at least 15% of the trial population are still at risk. It will be ascertained by the use of time-dependent period variables whether any potential treatment differences become larger over time, as well as testing for the interaction of log(time) and treatment. This will be done using a negative binomial model with SAS code similar to the following or equivalent code in another programming language such as R:

```
PROC GENMOD DATA=events;
  CLASS treatment(ref='Placebo') <trial part & randomization plan>
      <time period> sex race/ethnicity region;
  MODEL <number of events> =
      treatment <time period> treatment*<time period>
      <trial part & randomization plan>
      age sex race/ethnicity region / DIST=NB LINK=LOG LRCI
      OFFSET=<log time at risk in time period> ;
  REPEATED SUBJECT=subject / TYPE=UNSTR WITHINSUBJECT=<time period>;
RUN;
```

Subgroups that might be at higher risk (e.g. elderly, diabetic status, patients with low baseline neutrophil counts, smoking history, alcohol history, comorbidities and region) will be looked at and treatment by covariate interactions will be evaluated. It will be explored what factors pre-dispose patients towards infections or repeated infections in this population.

It will be explored whether any potential risk of infections changes based on whether patients have reported a vaccination within 3 months or at all at baseline (test for interaction term), this will also be done for the 6 month time frame by whether vaccinations were live-vaccinations or not (live vaccinations within 3 months were not permitted in this study). Additional predictors of infections in this population will be explored.

Serious infections and malignancies will be adjudicated and the adjudication results will be reported.

Duration of infections

To investigate whether the duration of infections is affected by canakinumab, exploratory observational analyses of a non-randomized nature will be conducted despite the inherent biases that cannot be excluded in such situations. Patients in canakinumab groups and placebo matched on the MedDRA preferred term for the infection, time since index MI, age at time of infection, sex, race/ethnicity and region will be compared using negative binomial regression. This will also be done on a high level and low level term basis, because less specific terms might allow more patients to be compared giving more power, but at the same time might make the infections less comparable. Besides the length of infections, the severity/seriousness and the necessary actions will also be compared. As a further analysis, covariate adjustments will be made for age, sex, race/ethnicity, region, BMI, neutrophil count, smoking/alcohol history, diabetic status, time since index MI and trial part, while the natural logarithm of (CV endpoint censoring date or for patients with AEs date of first AE of type under analysis – randomization date + 1 day) will be used as an offset variable.

7.4.2 Liver safety data

Presentation of liver safety data will follow the internal Novartis standards for liver safety analyses. The risk of liver toxicities will be quantified and described in terms of onset, dose, duration and severity.

The liver toxicity (LFT abnormality) will be identified with the Adverse Event (SOC Hepatobiliary disorders and the hepatic disorder SMQs, narrow search), and the laboratory parameters mainly AST (aspartate aminotransferase; also known as SGOT), ALT (alanine aminotransferase; also known as SGPT), ALP (alkaline phosphatase) and TBL (total bilirubin; conjugated (direct) (DBL) and unconjugated (indirect) bilirubin).

All analyses (whether e.g. Cox regression, analysis of covariance or ordinal regression) will take into account baseline log ALT, log AST, log TBL, log direct bilirubin values, alcohol use, age, sex, race/ethnicity and region as long as the number of events allows it.

Criterion-based "event" tables

Threshold values of interest for liver function tests are given below.

Table 7-3 Liver-related events

Parameter	Criterion
ALT	>3xULN; >5xULN; >8xULN; >10xULN
AST	>3xULN; >5xULN; >8xULN; >10xULN
ALT or AST	>3xULN; >5xULN; >8xULN; >10xULN
TBL	>1.5xULN; >2xULN
DBL	>1.5xULN; >2xULN
TBL and DBL	TBL>1.5xULN+(DBL>ULN,>1.5xULN or >2xULN)
	TBL>2x ULN+(DBL>ULN, >1.5xULN or >2xULN)
ALP	>2xULN; >3xULN
(ALT or AST) & (TBL or DBL)	ALT or AST >3xULN & TBL or DBL >2xULN
	ALT or AST >5xULN & TBL or DBL >2xULN
	ALT or AST >10xULN & TBL or DBL >2xULN
ALP & (TBL or DBL)	ALP >3xULN & TBL or DBL >2xULN
(ALT or AST) & (TBL or DBL) & ALP	AT >3xULN & TBL or DBL > 2xULN & ALP < 2xULN (potential Hy's Law case)
	Note: elevated ALP may suggest obstruction as a consequence of gall bladder or bile duct disease; ALP may also be increased in malignancy. FDA therefore terms Hy's Law cases as indicators of pure hepatocellular injury. This does not mean that cases of AT >3xULN & TBL >2xULN & ALP ≥ 2xULN may not result in severe drug-induced liver injury (DILI).

AST = Aspartate aminotransferase; also known as SGOT, ALT = Alanine aminotransferase; also known as SGPT, ALP = Alkaline phosphatase, TBL = Total bilirubin, DBL = conjugated (direct) bilirubin

The laboratory results meeting specified criteria standard table will be used to provide the number and percentage of patients having AST, ALT > 3, 5, 8, 10 x ULN or TBL >1.5, 2 x ULN or ALP > 2, 3 x ULN.

The number and percentage of potential Hy's Law cases will be presented by treatment group. Potential Hy's Law cases are defined as those patients with AST, ALT >3xULN & TBL >2xULN & ALP <2xULN at the same lab measurement.

Shift-tables

A cross-tabulation of baseline and worst post-baseline values by below, within and above normal range categories will be provided. Shift tables will be provided for the parameters AST, ALT, TBL, direct bilirubin and ALP. These summaries will be presented by laboratory test and treatment group.

Standard laboratory change from baseline tables

The lab standard tables will be produced on all the laboratory parameters including changes from baseline in liver parameters. Continuous liver function test values will be plotted over time and analyses of covariance adjusting for covariates will also be performed.

SMQ, lower level SMQs standard table and preferred term standard table

The following SMQ and lower level SMQs will be presented including the respective preferred term frequencies covered under the SMQs:

- "Possible drug related hepatic disorders – comprehensive search" (broad search, mandatory)

The corresponding narrow SMQs will also be analyzed.

Notable events may be defined as liver-related death (Non-cardiovascular death due to liver failure); liver transplantation (from the SAEs and AEs); liver-related study drug discontinuation (from the AEs); any of the 3 events.

The Cox risk of the hepatic disorder SMQ and of the SOC Hepatobiliary disorders on each of the active treatment dosages relative to control will be calculated with 95% confidence intervals.

The standard SMQ-PT table will be used to provide the number and percentage of patients with hepatic disorders.

Ordinal regression approach

A proportional odds model will be fitted with each subject's response to be trichotomized, i.e.

0. ALT and AST < 3xULN ("no signal"),
1. ALT or AST ≥ 3xULN but ALT and AST < 5xULT ("mild signal"), or
2. ALT or AST ≥ 5xULN ("signal")

and each covariate baseline ALT, baseline AST, alcohol use, smoking history, age, sex, race/ethnicity, trial part/randomization plan and treatment group to be modeled as a fixed effect. The log of the number of visits with an ALT/AST sample will be used as an offset variable. SAS code similar to the following will be used to fit this model (or equivalent code in another programming language such as R):

```
PROC LOGISTIC DATA=dataset;
  CLASS alcohol smoking sex race/ethnicity region
      <trial part/randomization plan> treatment(ref='Placebo');
  MODEL <ALT/AST category> = alcohol smoking sex race age region
      <trial part/randomization plan> treatment
      <baseline log ALT, AST, TBIL and direct bilirubin>
      / DESCENDING CLODDS=PL LINK=CLOGIT SCALE=NONE AGGREGATE
        OFFSET=<log duration of follow-up for laboratory endpoints>;
  UNITS age=10;
```

```
RUN;
```

The duration of follow-up for laboratory endpoints will be based on the total duration including time after a potential elevation. Should the proportionality assumption in the model above appear to be strongly violated a sensitivity CMH test with modified ridit scores will be performed. Time to elevations will also be analyzed using a discrete time Cox regression model.

Graphical displays

For all patients with liver values (AST, ALT, ALP, TBL) matching the thresholds of 5xULN and Hy's Law (Table 2.9-3), single patient LFT profile graphs will be generated showing all AST, ALT, ALP, TBL lab values reported for this study and the time of study treatment for these patients. An evaluation of Drug Induced Serious Hepatotoxicity (eDISH) plot will also be created.

7.4.3 Malignancy

Occurrence of malignancies as confirmed by the blinded adjudication committee will be summarized based on the adjudication according whether they are

- Primary type (by MedDRA high level group term/high level term including secondary paths and preferred terms)
- Newly detected or represent an existing malignancy
- Whether the patient's history includes this malignancy
- Evidence of metastases and their stage
- Whether the presentation was considered typical or atypical
- Whether and which risk factors there were
- Whether the malignancy was considered expected, uncommon, but not unexpected or rare or unusual
- Assessment of response to therapy

Malignancies from adverse event reports will be identified using the narrow SMQ Malignancies and its sub-SMQs. They will be reported as part of the safety analyses described in section 7.3.1. Preferred terms, as well as high level term classifications including secondary paths will be reported to allow assessment of the occurrence of malignancies by site. Time-to-event analyses will be conducted and Kaplan-Meier type plots will be presented. This will also be done for non-cardiovascular deaths due to malignancy.

To assess whether there is an imbalance when follow-up becomes longer, time by treatment interactions will be explored looking at <= 2 years of follow-up versus >2 years of follow-up, as well as other possible cut-offs.

The potential for confounding due to for example competing risks in a situation where canakinumab reduces CV or overall mortality will be evaluated.

7.4.4 Thrombocytopenia

Effects with respect to thrombocytopenia will be assessed by the laboratory analyses described in section 7.3.2, additionally decreased platelet counts per CTC grades as shown in table 7-4 will be reported and baseline platelet counts will be taken into account in this analysis. Shifts versus baseline will also be shown per CTC grade.

Table 7-4 NIH CTC version 4.0 grades for platelets

CTC terms	Grade 1	Grade 2	Grade 3	Grade 4
Platelet count decreased	<LLN-75,000/mm^3; <LLN-75.0 x 10^9/L	<75,000-50,000/mm^3; <75.0 - 50.0 x 10^9/L	<50,000 - 25,000/ mm^3; <50.0 - 25.0 x 10^9/L	<25,000/mm^3; <25.0 x 10^9/L

As severe thrombocytopenia could potentially lead to serious bleeding adverse events fulfilling the narrow and broad Haemorrhages SMQ will be summarized including the sub-SMQs Haemorrhage laboratory terms and Haemorrhage terms (excl laboratory terms) by seriousness and severity.

The occurrence of the Haemorrhages SMQ will be analyzed using Cox regression as described in section 7.2 also adding the baseline platelet count to the model and looking for an interaction with treatment.

Whether early drops in platelet counts (or thrombocytopenia) are indicative of subsequent bleeding events will be explored.

Whether baseline thrombocytopenia or early drops in platelet counts (or thrombocytopenia) are indicative of subsequent bleeding events will be explored.

The baseline use of antithrombotic medications will be evaluated as a subgroup and treatment by subgroup interactions will be evaluated for both the occurrence thrombocytopenia and bleeding events.

Whether platelet count differences, occurrences of CTC grades or occurrence of bleeding events change over time will be assessed both graphically, as well as using negative binomial regression (for the occurrence of bleeding events or abnormalities of at least a certain CTC grade) as described in section 7.2 and a repeated measures analysis of the continuous platelet counts with a time by treatment interaction.

It will be explored what factors pre-dispose patients towards thrombocytopenia in this population using Cox regression.

7.4.5 Neutropenia

Drug effects on neutrophils will be assessed by the laboratory analyses described in section 7.3.2, additionally decreased neutrophil counts (occurrence of neutropenia) per CTC grades as shown in table 7-5 will be reported and baseline neutrophil / white blood cell counts will be taken into account in this analysis. Shifts versus baseline will also be shown per CTC grade.

Whether baseline neutropenia or early drops in neutrophil counts (or neutropenia) are indicative of subsequent infections will be explored.

Table 7-5 NIH CTC version 4.0 grades for neutrophils

CTC terms	Grade 1	Grade 2	Grade 3	Grade 4
Neutrophil count decreased	<LLN - 1500/mm^3; <LLN - 1.5 x 10^9/L	<1500 - 1000/mm^3; <1.5 - 1.0 x 10^9/L	<1000 - 500/mm^3; <1.0 - 0.5 x 10^9/L	<500/mm3; <0.5 x 10^9/L

Whether neutrophil differences or occurrences of CTC grades change over time will be assessed both graphically, as well as using negative binomial regression (for the occurrence of abnormalities of at least a certain CTC grade) as described in section 7.2 and a repeated measures analysis of the continuous neutrophil data with a time by treatment interaction.

The number of patients that discontinued treatment and then returned to normal values or did not return to normal values, as well as those that did not discontinue and then returned to normal values or did not return to normal values will be summarized.

It will be explored what factors pre-dispose patients towards neutropenia in this population using Cox regression.

7.4.6 Immunogenicity/allergenicity

Immunogenicity/allergenicity adverse events will be identified using a list of search criteria to be provided by the Novartis Brand Safety Leader, which will be stored in CREDI. These adverse events will be looked at overall and only looking at adverse events within 7 days following each subcutaneous injection.

Additionally, the number (%) of patients with positive anti-canakinumab antibodies will be reported and it will be explored whether the occurrence of positive anti-canakinumab antibodies is associated with subsequent immunogenicity/allergenicity adverse events.

7.4.7 Hypercholesterolemia

Drug effects on lipids will be assessed by the laboratory analyses described in section 7.3.2. CV outcomes are the primary endpoint of this study and sub-group analyses for CV outcomes by baseline lipid values are planned (see section 2.2). Additionally, the dose of statins used will be tracked as described in section 5.

7.4.8 Long term effects on kidney function

Drug effects on eGFR and the urine albumin/creatinine ratio will be assessed by the laboratory analyses described in section 7.3.2 and AE reports. Patients' worst CTC classifications as per table 7-6 at any point during the study will also be provided.

The number of patients with eGFR declines compared to baseline of ≥ 25%, ≥ 40% or ≥ 50%, or by ≥ 30 ml/min/1.73 m^2 at any point in the study will be summarized as well as those with serum creatinine increases compared to baseline of ≥ 50%, ≥ 0.5 mg/dL, ≥ 2.0 mg/dL, ≥ 2.5 mg/dL or ≥ 3.0 mg/dL.

Time to nephropathy in terms of urine albumin/creatinine ratio (≥ 30 mg/mmol) will be assessed.

Additionally, the occurrence of nephropathy based on adverse event reporting, occurrence of the narrow SMQ Acute Renal Failure, doubling of serum creatinine, endstage renal disease (ESRD) defined as dialysis, renal transplant, or serum creatinine >530 µmol/L (6.0 mg/dL)

and time to non-cardiovascular death due to renal failure will also be analyzed. An overall composite will also be provided. The continuous log-transformed urine albumin creatinine ratio will be also analyzed as well as eGFR over time and abnormalities will be considered. See also section 7.4.8.

Predictive covariates will be taken into account in all models including baseline eGFR, baseline creatinine, baseline log urine albumin creatinine ratio, age, sex, race/ethnicity, baseline blood pressure, history of heart failure, antihypertensive drug use and baseline glycemic status.

Table 7-6 NIH CTC version 4.0 grades for Chronic kidney disease, which can be assessed in this trial

CTC terms	Grade 1	Grade 2	Grade 3	Grade 4
Chronic kidney disease	eGFR† <LLN - 60 ml/min/1.73 m^2	eGFR† 59 - 30 ml/min/1.73 m^2	eGFR† 29 - 15 ml/min/1.73 m^2	eGFR† <15 ml/min/1.73 m^2; dialysis or renal transplant indicated*

† CrCl not assessed in this study

* in this study to be defined as report of kidney transplant or dialysis as non-drug therapy

7.4.9 QT prolongation

The routine risk of QT prolongation will be evaluated as described in section 7.3.4.

7.4.10 Other adverse events of special interest

The following adverse events of special interest will be identified using a list of search criteria to be provided by the Novartis Brand Safety Leader, which will be stored in CREDI:

- Injection site reactions (including injection site reactions leading to discontinuation, by severity and whether they were SAEs)
- Lymphoid organ toxicity
- Vertigo (by severity and seriousness)
- Autoimmunity reactions (by severity and seriousness, also occurrence at ANA antibodies by the end of the study)

They will be reported by severity and seriousness.

Additionally, immunogenicity data obtained together with PK data will be analyzed.

Changes from baseline in systolic and diastolic blood pressure, the occurrence of hypertension, blood pressure abnormalities and the degree of blood pressure control will be analyzed based on the regularly collected SBP and DBP data. Additionally, occurrence of adverse events of interest (e.g. malignant or treatment-resistant hypertension) will be summarized. Such analyses will take into account age, sex, race/ethnicity, region and baseline blood pressure. Baseline blood pressure by treatment interactions will be investigated.

7.4.11 Hypoglycemia

As per the draft FDA requirements for the evaluation of prevention of diabetes, rates of hypoglycemia will be compared statistically between groups. Hypoglycemic events will be

identified using the Novartis MedDRA Query (NMQ) for Hypoglycemia or – if it becomes available – the corresponding SMQ. Comparisons between treatment groups will be both done as time to first event analyses (including reporting the number of affected patients), as well as analyzing count data (episodes per subject years of follow-up, number of patients with a certain number of hypoglycemic episodes – i.e. none, 1 episode, 2 episodes etc.) using negative binomial regression as described in section 7.2. Baseline glucose and HbA1c values will be used as covariates in analyses.

Such reporting will be done for all hypoglycemic events as well as for events classified as severe by the investigator and events classified by the investigator as SAEs, Any information on potential precipitants and patterns identified in further analyses will also be reported.

8 Interim analyses

Interim analyses of efficacy, futility and safety will be carried out during the study. Two interim analyses of efficacy will be performed when about 50% of the target number of primary cardiovascular events have been accumulated and the second one when 75% of the planned number of events are available. Criteria for the interim and final analyses will be determined using a fixed Bonferroni split of the alpha allocated to the interim analyses and to the final analyses in order to protect the overall one-sided familywise type I error rate across all analyses at 2.5%. The fixed total one-sided alpha allocated to both interim analyses of efficacy combined is 0.05%. Of this 0.01% is allocated to the first efficacy interim analysis and 0.04% allocated to the second efficacy interim analysis. The one-sided significance level for the final analysis is thus 2.45%.

Interim analyses for futility will be conducted simultaneously with the two analyses of efficacy. It should be noted that the efficacy criteria are not modified to “buy back” alpha based upon the presence of futility boundaries; this conservative approach ensures that the familywise type I error rate of the study is protected.

Full details on boundaries and stopping rules will be pre-specified in the Charter of the Data Monitoring Committee (DMC). Timing and number of safety analyses will also be specified in DMC charter.

Interim analysis will be performed by an independent academic statistical data analysis center at Brigham and Women’s Hospital (Massachusetts, USA) external to Novartis, who will not be involved in the trial conduct. The results will be reviewed by the Data Monitoring Committee (DMC).

Investigators, Novartis employees and others who are involved in the conduct of the trial and in the analysis of the final trial results, or who have contact with study centers, will remain blinded to the treatment codes and interim analysis results until all monitoring decisions have been made and the database has been locked for final analysis.

DMC

In CACZ885M2301, a DMC will monitor the trial’s progress, safety and efficacy on a regular basis or per the request of the DMC. Details regarding the reasons for the DMC and the

grounds for stopping/continuing trials, as well as the DMC procedures are provided in the DMC charter.

9 Sample size and power considerations

Sample size and power considerations are addressed in section 9.6 and 9.7 of the clinical trial protocol.

10 Pharmacodynamic and pharmacogenomics analyses

For PD evaluations

All FAS subjects with evaluable pharmacodynamic (PD) assessments will be included in the data analysis. Pharmacodynamic parameters will summarized over time. The hypothesis of treatment differences with respect to PD values will be evaluated at each timepoint individually, as well as overall using a repeated measures mixed effects model adjusting for treatment arm, trial part and region. Furthermore, the same model with additional baseline covariates will be applied to account for other factors. How predictive biomarkers are of outcomes will be evaluated using appropriate time to event methods such as the C-index including an exploratory evaluation of the best cutoff point to predict MACE in the study population. It will be explored to what extent pharmacodynamic parameters predict treatment benefit and whether the above analyses may have to be performed for each treatment arm individually. All tests will be two-sided and conducted at an $\alpha = 0.05$ level of significance. All CIs presented will be two-sided 95% CIs.

For PK / PD evaluations

All FAS subjects with evaluable PK and PD parameters will be included in the data analysis. The relationship between drug concentration and the pharmacodynamic variable will be examined by fitting PK-PD model.

Pharmacogenetics

Exploratory pharmacogenetic studies designed to investigate the association between genetic factors (genotypes) and clinical assessments (phenotypes) which are collected during the clinical trial will be conducted. Without prior evidence of a strong association, a number of possible associations will be evaluated with exploratory analyses. A range of statistical tests will be used for the analyses. Additional data, from subsequent clinical trials, may be needed to confirm associations. Alternatively, if the numbers of patients with Pharmacogenetic assessments enrolled in the study are too small to complete proper statistical analyses, these data may be combined, as appropriate, with those from other studies to enlarge the data set for analysis.

Pharmacogenomics

For pharmacogenomics, messenger RNA (mRNA) will be extracted from blood samples. mRNA will be analyzed for gene expression using gene expression microarrays such as Affymetrix microarray technology and/or quantitative RT-PCR. Quality control of all

individual RNA samples and expression data will be conducted. The gene expression data will be analyzed using several different algorithms.

11 PK/PD analyses, modeling and simulation

Dose-exposure-response modeling will be used to characterize the effects of canakinumab on the target, Il-1β and biomarkers such as CRP and Il-6. The PK – Il-1β relationship can be described by antibody-ligand binding models. The response of biomarkers such as CRP and Il-6 will be analyzed through PKPD modeling by exploring concentration-response relationships for canakinumab and Il-1β with downstream biomarkers.

The correlation between the response in some of these biomarkers with subsequent treatment outcomes (i.e. biomarker assessments predicting occurrence of future endpoints) will be examined. The existence of such relationships will help in understanding the relationship between doses/dosing regimens and clinical (especially cardiovascular) outcomes.

Appendix 1: Glucose and glycated hemoglobin changes over time and the washout period

Introduction and rationale for analyses

The key secondary new onset of diabetes endpoint will also be supported by analyses using data from the study's washout period. As these analyses will only be conducted after the washout – i.e. after the main part of the trial has already been reported – and require extensive detailed pre-specification, their description has been moved to this appendix to the statistical analysis plan.

Glucose and glycated hemoglobin changes over time for the overall study group with pre-diabetes at baseline from the double-blind phase and the washout period will be combined to assess to what extent canakinumab truly delayed progression to diabetes and to what extent it only transiently masked diabetes during double-blind treatment. The analysis will take into account that masking of diabetes may have occurred in patients not diagnosed as diabetic during the core study that did not enter the washout period. A number of sensitivity analyses with a range of assumptions about these patients will be performed.

The FDA draft Guidance for Industry on "Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention" explains that it is important to establish "improvement in clinical parameters beyond those that would be expected from glucose lowering alone" in case that there are fewer new Type 2 diabetes diagnoses with a glucose lowering drug than with placebo. For this purpose the draft guidance mentions two options, which will be addressed as described below.

According to the draft guidance one option would require a delay or lessening in microvascular or macrovascular complications. A reduction in diabetic complications such as nephropathy, retinopathy, neuropathy or cardiovascular events would constitute a clear benefit to patients irrespective of whether it occurred due to a delay/prevention of diabetes or simply due to better glycemic control. Concerning microvascular complications, the present trial is neither designed nor powered to show that the intervention leads to reductions in these events.

The expected duration of follow-up of at most 5 years makes it unlikely that effects on microvascular complications in patients starting trial follow-up in a pre-diabetic state could be detected, even with a much larger sample size than available in the present trial. It is also unlikely that the planned long term follow-up after the end of the double blind intervention will suffice to show an impact on microvascular events due to the slow progression of such complications in patients with Type 2 diabetes. Regarding reductions in cardiovascular events, the question as to what extent a cardiovascular benefit might derive from delay or prevention of diabetes might at best be indirectly answered by comparing the treatment effect on cardiovascular events between normoglycemic, at risk for diabetes and diabetic patients.

Nevertheless, diabetic complications will be analyzed using adverse event reporting of these events as described in section 6.3.4 in those at risk for diabetes (as well as diabetic) patients, since any reductions in such events would constitute a clear benefit to patients. Additionally it will be assessed whether there is any reduction in the number of patients developing insulin dependent diabetes amongst initially pre-diabetic or diabetic patients on the basis of the reported concomitant medications.

The other option for establishing "improvement in clinical parameters beyond those that would be expected from glucose lowering alone" mentioned by the draft guidance for industry on "Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention" is to demonstrate a "durable delay in the onset of Type 2 diabetes after the prevention therapy is stopped" in order to exclude the possibility that progression to diabetes was solely masked through direct glucose lowering. This is what the present trial has been designed to assess primarily based on the fasting plasma glucose and glycated hemoglobin assessments throughout the main trial and the proposed washout period. A number of analyses supportive of the key secondary new onset of diabetes endpoint will be conducted that taken together may allow a reasonable assessment of whether such a durable delay occurred.

Washout period disposition

The number of patients eligible to enter the washout period, the number of patients entering it, the number not entering it (including reasons), the number completing the washout period and the actual length of washout will be summarized by treatment group.

Summary statistics

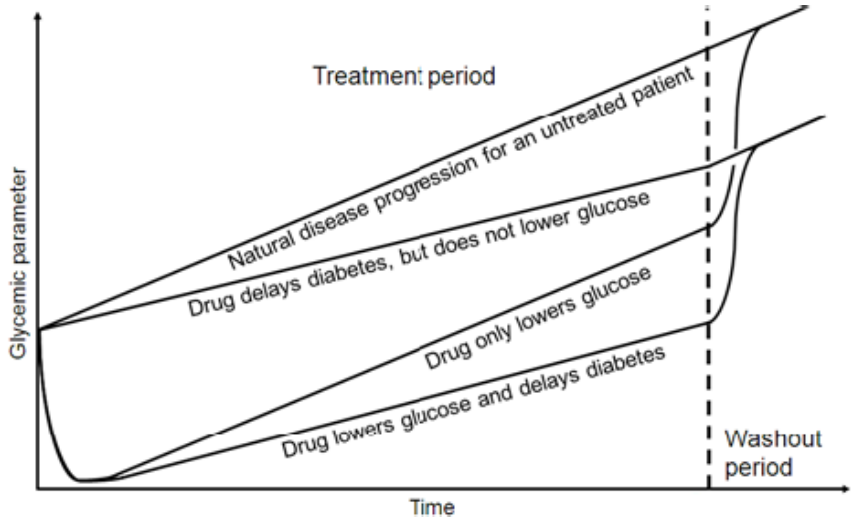
The number of patients diagnosed as diabetic in the main trial and in the washout will be summarized descriptively by treatment group. Glycemic parameters at the end of the washout will be summarized by treatment group overall, compared to baseline and compared to the final main study visit. This will include considering the subgroup of patients that entered the washout but had stopped study medication prior to the final main trial assessment.

Repeated measures mixed effects disease progression model

The continuous longitudinal HbA1c and separately the continuous FPG values over time will be assessed. Doing so across the main trial and the washout period appears to be the most appropriate way to further investigate the mechanism by which a potential reduction in the key secondary endpoint of new-onset diabetes diagnoses may have occurred.

The continuous longitudinal HbA1c and separately the continuous FPG will be analyzed using a mixed effects repeated measures disease progression model. The key assumptions of the proposed model are illustrated in Figure A1-1.

Figure A1-1 Schematic representation of possible drug effects



The model is similar to a model described by Bhattaram et al. (2009) in the Parkinson's disease setting and was adapted to the diabetes setting based on the discussion by Buchanan (2007) on what type 2 diabetes prevention means. Any "true" diabetes prevention through a modification of the underlying process of progression towards diabetes would be assumed to decrease the slope of the increase over time in glycemic values, but could perhaps alternatively also take the form of rapidly occurring lower glucose values that persist upon washout of the drug. Untreated patients would be assumed to have on average linearly increasing glycemic values, at least across the limited pre-diabetic range. Any direct pharmacological improvement of glycemic values by a drug ("masking") would be assumed to induce a downward shift, but would not affect the slope relative to the slope of placebo. This effect would be expected to disappear after a sufficiently long washout.

However, it is clear that the interpretation of the effects estimated from such a model would have to be made in the context of the totality of the data and that demonstrating a change in slope does not by default equate to demonstrating a delay or the prevention of diabetes. This is because a change of slope for a glycemic measurement might also indicate a direct pharmacological glucose lowering (masking) effect that becomes larger as disease progresses.

Additional analyses, e.g. subgroup analyses by baseline FPG and HbA1c levels, investigating treatment by time by baseline value interactions etc. will be conducted to clarify which interpretation of the results would be the most appropriate. In this respect, approaches other than a washout (e.g. re-randomization, randomized withdrawal) may provide additional insights.

Primary mixed effects model for main study and washout data

The chosen repeated measures mixed effects disease progression model will be used to model post-baseline HbA1c and FPG up to the date of progression to diabetes – with data thereafter imputed as described in the next sub-section – for the three doses of canakinumab versus placebo. It will contain model terms for

- slope term for time representing a linear impact of disease progression on glycemic values (also as a random effect representing slope for each subject),
- a potential flattening of the disease progression slope on each of the three doses as treatment by time interaction term (with an impact that remains present after the washout),
- a direct glucose lowering effect of each of the three canakinumab doses on glycemic values (constant downward shift) as a main effect of treatment limited to the period of active treatment, which occurs outside the washout and does not persist after the washout,
- a lowering in glycemic values (constant downward shift) on each of the three canakinumab doses that persists after the washout as a main effect of treatment after washout,
- and other baseline covariates such as baseline FPG, baseline HbA1c, body mass index, family history of diabetes, exercise (rarely/never, less than once a week, once a week, 2-3 times a week, 4-6 times a week, daily), region, linear log baseline hsCRP and time since index MI. These are baseline covariates that are either expected to be relatively strongly predictive of post-baseline glycemic values or in the case of time since index MI a stratification factor used in the randomization.

As HbA1c reflects the glucose levels over the preceding 8-12 weeks, the 2 week and 1.5 month HbA1c measurements will not be used in this model. This ensures that the delayed impact of lowered glucose values on HbA1c is not confused with change in the slope of HbA1c values potentially indicative of a delay in the development of diabetes. A number of covariance structures may be appropriate and different ones will be evaluated, for example an unstructured variance-covariance matrix was recommended by Mallinckrod et al. (2004). The denominator degrees of freedom will be calculated using the Kenward-Roger method and the observed information matrix of the covariance parameter estimates will be used.

SAS code similar to the following will be used for a model with random slopes (or equivalent code in another programming language such as R)

```
PROC MIXED;
        BY imputation <parameter under analysis: FPG or HbA1c>;
        ** washout = flag for whether observation is from washout;
        CLASS treatment subject washout <time since index MI>;
        MODEL value = treatment <visit month> treatment*<visit month>
                washout treatment*washout
                baselineFPG baselineHbA1c BMI <time since index MI>
                <list of additional covariates>
```

/ DDFM=KR S;

RANDOM intercept <visit month> / SUBJECT=subject TYPE=UN;

RUN;

and similarly for a model without random slopes

PROC MIXED;

BY imputation parameter;

** washout = flag for whether observation is from washout;

CLASS treatment visit subject washout <time since index MI>;

MODEL value = treatment day treatment*day washout treatment*washout

baselineFPG baselineHbA1c BMI <time since index MI>

<list of additional covariates>

/ DDFM=KR S;

REPEATED visit / SUBJECT=subject TYPE=UN;

RUN;

Special considerations and missing data handling

Glycemic values after the diagnosis of diabetes may be confounded by the use of concomitant anti-diabetic medications (or any other physician intervention in reaction to the diabetes diagnosis) and glycemic values after the diagnosis of diabetes as confirmed by the adjudication committee are effectively missing as far as the availability of non-confounded assessments is concerned. Thus, they will be treated as such, as suggested in a similar setting by Murray and Findlay (1988). Simply analyzing data after diagnosis as per the intention-to-treat principle without taking this into account would otherwise "reward" a treatment group for achieving a sufficiently bad patient state that a physician intervenes. As a sensitivity analysis data will only be considered missing after the initiation of an anti-hyperglycemic agent (AHD).

Such missing values are missing at random (MAR), if the diabetes diagnosis is based on data recorded as part of the trial (Murray and Findlay 1988). This is also sometimes referred to as "deterministic MAR". I.e. the missing values are MAR given preceding values for both HbA1c and FPG including the repeat confirmatory measurements performed after the initially elevated measurements and information on diabetes diagnoses by other means, because this information determines that they are missing. Nevertheless, it would not be admissible to simply use likelihood methods e.g. on only the observed HbA1c data by itself. Doing so would only lead to valid frequentist inferences if any missing data were MAR given all preceding HbA1c values (Kenward and Molenberghs 1998), which is not the case as diabetes diagnoses could also have been based on FPG values or other information. For this reason, multiple imputation taking into account all preceding information including HbA1c and FPG values is an attractive and valid approach to deal with this kind of missingness (Rubin 1976 and Little and Rubin 1987). Multiple imputation will be used to impute all missing data from

the time of randomization to the last visit a patient would have had if he had completed the trial including the washout normally. The multiple imputation will be performed separately for each treatment group. The multiple imputation will be performed using the Markov Chain Monte Carlo (MCMC) method of Schafer (Schafer 1997) assuming multivariate normality. This can for example be done using the MCMC statement in the SAS procedure PROC MI with PROC MIXED results appropriately summarized across the multiple imputations using PROC MIANALYZE. As appropriate, data will be e.g. log-transformed prior to imputation to ensure a distribution closer to a normal distribution (see section 7.2 for a list of variables to be transformed) and then back transformed after imputation before performing the actual analysis. Estimates and confidence intervals will be calculated based on an appropriate number of multiple imputations to account for the between-imputation component of variability ensuring that the precision of estimates is not overstated. As a sensitivity analysis MCMC methods will also be used only to achieve a monotone missingness pattern and then both parametric regression methods (METHOD=REG option in the MONOTONE statement of PROC MI), or nonparametric methods based on propensity scores (METHOD=PROPENSITY option in the MONOTONE statement of PROC MI) will be used.

The number of imputations will be determined to be computationally feasible, and also to provide estimates of standard errors that provide an appropriate representation of the uncertainty present in the data. Just m=3 or 5 imputations may depending on the extent of missing data often be sufficient to ensure valid inference and appropriate coverage probabilities for confidence intervals. However, as described by Kenward and Carpenter (2007) and Graham et al. (2007) a number of e.g. m=200 imputations may result in narrower confidence intervals (more power) and estimates become more stable with respect to the choice of seed for pseudorandom number generation. This is the case especially when a large proportion of data is missing. Therefore, an as large as possible, but computationally feasible number of imputations, will be chosen based on experience with running these models close to the final database lock using dummy treatment codes.

As suggested by Liu and Gould (2002) post-baseline information that is potentially informative about why data are missing, namely

- time from randomization to date on which the missing value should have been assessed
- whether missing value would have been in the washout (washout observations to only be imputed for patients that were in principle eligible for the washout, but did not enter or complete it – a sensitivity analysis in this respect will be performed)
- previous and subsequent measurements of
  - both HbA1c and FPG including measurements to confirm diabetes
  - LDL, log HDL and log Triglycerides
  - log hsCRP
  - Vital signs: diastolic blood pressure, systolic blood pressure, BMI
- Gender, age, race/ethnicity, region, family history of diabetes, baseline smoking status, baseline alcohol use, baseline exercise (rarely/never, less than once a week, once a week, 2-3 times a week, 4-6 times a week, daily)
- Baseline medication use for all pre-specified medication classes (includes e.g. statins, beta blockers, renin-angiotensin-aldosterone system inhibitors or calcium channel blockers)

- Time since index MI
- Diagnosis of diabetes outside of the trial confirmed by the adjudication committee prior to an assessment (i.e. one indicator for each scheduled assessment of new onset of diabetes)

will be used in the imputation of missing data. Diagnoses of diabetes outside of the trial confirmed by the adjudication committee are used in imputation in order to come as close as possible to a MAR (given all data available for imputation) situation.

This approach should be much more appropriate than any single value imputation method such as e.g. last-observation-carried-forward (Siddiqui et al. 2009), which would be clearly inappropriate in the setting of a progressive disease.

In summary, our treatment of missing data reflects the concept that missing data will not be well represented by a single mechanism while specifically ensuring an appropriate treatment of missing data arising from physician intervention in response to diabetes diagnosis.

Further sensitivity analyses

Further sensitivity analyses will be performed as appropriate, based on suggestions from the academic community, from health authority or as needed based on the actual findings in the trial data. These will include both variations of the described model to assess violations of its assumptions, as well as using completely different approaches. For the latter purpose, for example, structural equation methods may be an option.

Within the existing model framework the sensitivity analyses shown in Table A1-1 will be performed.

Table A1-1 Sensitivity analyses in the specified model framework

Sensitivity analysis	Purpose
Data will only be considered missing after the initiation of an anti-hyperglycemic agent (AHD)	Assess impact of considering data (potentially too early) immediately following diabetes diagnosis as missing
Data at least 6 months after last dose treated as if it came from the washout	While for such cases the “washout” would not be per experimental design, direct glucose lowering effects should similarly disappear, which is potentially not correctly reflected in the primary model. This may provide non-negligible additional information in addition to the washout.
Time by baseline FPG, time by baseline HbA1c, baseline FPG by treatment, baseline HbA1c by treatment, treatment by time by baseline FPG, as well as Treatment by time by baseline HbA1c interaction added to model	Change of slope for a glycemic measurement might also indicate a direct pharmacological glucose lowering (masking) effect that becomes larger as disease progresses. The presence and size of any treatment by baseline and/or treatment by time by baseline interactions will allow an assessment of the presence and impact of such effects.
Subgroup analysis by quintiles of baseline FPG (and the same for baseline HbA1c)	Addresses similar questions as the analysis above.
2 week and 1.5 month HbA1c measurements included in the model (only for HbA1c model)	Assessment of the impact of excluding 2 week and 1.5 month HbA1c measurements from primary model.
Assessment of other covariance structures other than the unstructured one	If inspection of unstructured covariance matrix suggests that a more simple covariance structure may

Sensitivity analysis	Purpose
	be appropriate, then this may be a useful simplification of the model. Key other sensitivity analyses might then also be re-run with such a covariance structure.
Post-baseline weight at each assessment of glycemic parameters as a time-dependent model covariate. Also try additionally adding a year 1 effect (indicator for whether observations are from the first yet).	The use of post-baseline covariates requires caution, but this analysis may evaluate whether the time course in weight as a potential measure of lifestyle changes following trial entry explains any observed effects. Year 1 effect would potentially reflect a placebo or trial effect (e.g. stemming from regression to the mean or similar phenomena). Note that weight over time will be compared between treatment groups over time as described in section 7.3.3.
Longitudinal analysis of all values prior and post-progression to diabetes without any multiple imputation performed	Comparison to main analysis and better understanding of performance of multiple imputation, may however be an inappropriate analysis
Longitudinal analysis of all up to progression to diabetes without any multiple imputation performed	Comparison to main analysis and better understanding of performance of multiple imputation, may however be an inappropriate analysis
MCMC methods used only to achieve a monotone missingness pattern and then parametric regression methods for imputation	Assess impact of used MCMC imputation method
MCMC methods used only to achieve a monotone missingness pattern and then propensity score based nonparametric methods for imputation	Assess impact of used MCMC imputation method
Create hypothetical washout for all patients that did not complete the washout, whether they were eligible for it, or not.	Assesses impact of only imputing washout observations for patients that were eligible for the washout, but did not enter or complete it.

Unless otherwise specified these sensitivity analyses will be performed in the setting of the primary disease progression model for both FPG and HbA1c with and without random slopes following the described multiple imputation procedure.

Graphical displays of data

Several graphical displays of the data including glycemic values over time for study completers, for patients that have non-missing data up to each time-point, for all available data and for the imputed data will be shown. For data post-diabetes diagnosis actually observed data (potentially subject to physician intervention and other confounding) will be plotted versus the imputed data.

Changes to analyses in case of a randomized withdrawal instead of a washout

Were the washout period to be replaced with a re-randomization or randomized withdrawal, then analyses would largely be conducted in the same fashion as described above. Such other trial design choices other than a washout (e.g. re-randomization, randomized withdrawal) have been suggested, because they might for example provide additional insights with respect to the size of any direct glucose lowering effect. If such an approach were to be chosen, summary statistics would be displayed within main trial treatment group separately according to whether patients were re-randomized to receive active treatment or placebo. For the

primary mixed effects analysis model the washout indicator class variable would have an additional level to indicate the result of the re-randomization. I.e. it would have three levels: observation from main study, observation following re-randomization to active treatment, or observation following re-randomization to placebo.

Appendix 2: Post-stroke functional assessment sub-study

Full details of the planned analyses for the Stroke Functional Assessment Sub-study, will be specified separately, prior to completion of the first Interim analysis.

In line with the primary objective of the post-stroke functional assessment sub-study to evaluate whether canakinumab arms facilitate functional recovery from stroke, the primary endpoint for this sub-study is the modified Rankin scale assessment 90 days post-stroke. Further endpoints are the 30 day results of the modified Rankin scale assessment, the 30 and 90 day MFSI-SF and the 30 and 90 day SIS-16.

Note that while patients were initially randomly assigned to treatments, the subset of patients experiencing a stroke may represent a biased subset. The impact of the occurrence of fatal strokes in the main study on the results of the sub-study also needs to be considered.

Besides basic summary statistics the main study report will report an intention-to-treat analysis that will rank patients from best to worse as

- alive at trial end and no stroke,
- alive at trial end and stroke with best Rankin scale (similarly also MFSI-SF/SIS-16)
- …
- alive at trial end and stroke with worst Rankin scale (similarly also MFSI-SF/SIS-16)
- dead at trial end

Ranking within these categories will be done with earlier stroke/death being worse than a stroke/death occurring later.

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Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) - A randomized, double-blind, placebo-controlled, event driven trial of quarterly subcutaneous canakinumab in the prevention of recurrent cardiovascular events among stable post-myocardial infarction patients with elevated hsCRP

Detailed Statistical Methodology

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List of acronyms

AE	Adverse event
AHD	Antihyperglycemic drug
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase (SGPT)
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical classification system
BCa	Bias-corrected and accelerated bootstrap
BMI	Body Mass Index
BNP	Brain Natriuretic Peptide
BWH	Brigham and Women's Hospital
CABG	Coronary Artery Bypass Graft
CAD	Coronary artery disease
CANTOS	Canakinumab Anti-inflammatory Thrombosis Outcomes Study
CCU	critical care unit
CDBL	Clinical Database Log
CEC	Clinical Events Committee
CHD	Coronary Heart Disease
COPD	Chronic Obstructive Pulmonary Disease
CREDI	Novartis Clinical REsearch Documentation and Information system
CRF	Case Report Form
CRS	Case Retrieval Strategy
CV	Cardiovascular
DBL	Conjugated (direct) bilirubin
DBP	Diastolic Blood Pressure
DHP	Data Handling Plan
DILI	Drug-induced liver injury
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eGFR	estimated Glomerular Filtration Rate
FAS	Full Analysis Set
FPG	Fasting Plasma Glucose
HbA1c	Glycosylated hemoglobin
HDL	High Density Lipoprotein
HR	Heart Rate
hsCRP	high sensitivity C-reactive protein
ICU	intensive care unit
IDL	Intermediate density lipoprotein
Il-1β / Il-6	Interleukin-1β, Interleukin-6
IRT	Interactive Response Technology
IP	Investigational Product
IVRS	Interactive Voice Response System
LAD	Left Anterior Descending artery
LCX	left circumflex artery
LDL	Low Density Lipoprotein
LFT	Liver Function Test
LLN	Lower Limit of the Normal range
LPLV	Last Patient Last Visit
MACE	Major Adverse Cardiovascular Events (CV death, MI or stroke)
MAR	Missing At Random

MCMC	Markov chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
NMQ	Novartis MedDRA Query
NOD	New Onset Diabetes
NovDTD	Novartis Drug/Therapy Dictionary
NT-proBNP	N-terminal pro-Brain Natriuretic Peptide
OC/RDC	Novartis Oracle Clinical/Remote Data Capture system
PCI	Percutaneous Coronary Intervention
PD	Protocol Deviation or Pharmacodynamics
PG/PGx	Pharmacogenomic
PK	Pharmacokinetics
PPS	Per-Protocol Set
PT	MedDRA Preferred Term
QTc	heart rate-corrected QT interval
QTcB	QTc (Bazett's correction)
QTcF	QTc (Fridericia's correction)
RAAS	Renin-angiotensin-aldosterone system
RCA	Right coronary artery
RMP	Novartis Risk Management Plan
SAE	Serious Adverse Event
SAF	Safety Set
SBP	Systolic Blood Pressure
SMQ	Standardized MedDRA query
SOC	(primary) System Organ Class
SPP	Novartis Safety Profiling Plan
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TBL	Total bilirubin
TIA	Transient Ischemic Attack
TNF	Tumor necrosis factors
VAS	Visual analogue scale
VLDL	Very low-density lipoprotein

Document History – Changes compared to previous versions of RAP module 3

Amendment 4, April 14, 2017

Section	Changes
2.1	Table 2-1: Addition of PD for site closure due to GCP non-compliance
2.2	Table 2.3-1 Age subgroup categories clarified to make clear that these are two separate subgroup variables
2.2	Table 2.3-1: Added subgroup as requested by FDA (presence of MI prior to index MI – yes/no)
2.2	Table 2.3-2 Change made Age subgroup categories to clarify this is two separate subgroup variables (consistent with Table 2.3-1)
2.3.1	Added text to highlight different terminology used in the protocol
2.3.8	Amended to reflect that the LPLV date will be used as the cut-off date since all events are planned to be adjudicated up to the last patients' visit
5	Removed Table 5-1. Revised text referencing table 5-1 to state that summaries should be based on the protocol visit schedule. Updated references to Table 5-2 due to table re-numbering.

Amendment 3, July 19, 2016

Section	Changes
Various	Various changes to text are made to clarify the intent. Minor changes are not reflected below. Changes that result in a change from what was originally intended are explained below.
1	Changed wording to reflect that the data from the washout and extension phases of the study will be addressed in a separate analysis plan and study report.
2.2	Table 2.3-3: removed subgroup related to patients entering washout who had stopped medication prior to final main trial assessment.
2.3.8	Clarifying that the analysis cutoff date could be earlier than the LPLV. In this case, events will only be considered as investigator reported.
2.3.9	- Removed planned sensitivity analyses for examining the assumption of non-informative censoring. This will be investigated, but not generally included in the study report. - Clarified that censoring date may not be the same for all time to event endpoints.
2.4	Figure 2-3 updated to match corresponding figure in study protocol.
5	Definitions of medication categories updated.
6	Removing the text about "post treatment phase" as it was resulting in confusion as to what was intended. Clarified main analyses will be based events occurring in the double blind phase.
6.1.2	Updated censoring algorithm to align with use of the cutoff date.
6.3.1	- Covariate adjusted analysis of primary endpoint changed to "may be considered." This is an exploratory analysis and not planned to be part of the study report. - Added that the association between hsCRP changes and outcomes will be explored, this is already mentioned in the current protocol.
6.3.2	- Added supportive analyses for diabetes related time to event endpoints. - Removed reference to analysis of washout period data. - Added statement that washout period data will be analyzed in a separate study

Section	Changes
	report or an addendum to the study report.
6.3.4	- Added text so that analyses will be dependent on number of events. - Removed text related to competing risks analysis.
6.5	Dose response model approach revised to reflect current plan for dose response modelling.
7	- Removed text related to summarizing data by trial part to avoid confusion between the main AE tables, which are pooled across trial parts and some specific analyses that present data separately by trial part. - Revised categories used for by-time-period analyses.
7.3.1	- Clarified on-treatment definition for AEs. - Removed plan for time-to-event analysis or AEs.
7.3.2	- Updated notable criteria in Table 7-1. - Added detailed description for analysis of long term effects on kidney function.
7.4	Updated list of adverse events of special interest to align with current safety profiling plan.
7.4.1	- Added by-time-period analyses for infections to align with other adverse event analyses. - Model for analysis of infections is revised to align with model for other adverse event analyses. - Analysis of duration of infections revised to only present a descriptive summary. Negative binomial model analysis is removed.
7.4.2	Removed ordinal regression analysis of LFT parameters; results are summarized using frequency tables.
7.4.3	Additional summary tables added to align with other adverse event analyses.
7.4.4	Removed summary of early drops in platelet counts.
7.4.8 – 7.4.12	- Topic of long term effects on kidney function was moved into Section 7.4.12 (Other safety topics). Analysis description is covered in section 7.3.2. (Laboratory data). - Topic of QT prolongation was moved into section 7.4.12 (Other Safety topics) and will be analyzed under section 7.3.4 (ECG). - Section on Hypoglycemia reordered to section 7.4.8. - Added new sections 7.4.9-7.4.11 (Autoimmunity reactions; Injection site reactions; Vertigo/dizziness). - Section on “Other safety topics” reordred to section 7.4.12. Section title changed to clarify that this section addresses other adverse events that are not part of the adverse events of special interest.
10	Removed; this will be addressed in a separate analysis plan and report.
11	Removed; this will be addressed in a separate analysis plan and report.
Appendix 1	Removed; this will be addressed in a separate analysis plan and report.
Appendix 2	Renumbered to Appendix 1.

Amendment 2, April 13, 2016

Section	Changes
Throughout	Editorial changes.
2.1 (Table 2-2)	Updated Per protocol criteria.
2.2 (Table 2.3-1)	- Detail added on the region subgroups.

Section	Changes
	- Clarified analyses would be done in all tables by region subgroup. - Updated definition of Pre-diabetic and Diabetic.
2.2 (Table 2.3-3)	- Details added to basis for diabetes diagnosis subgroups - Baseline HbA1c/FPG categories subgroups updated.
2.3.4	On-treatment definition added.
2.3.9 (previously 2.3.8)	- Added missing date imputation rules. - Amended time to event section. - MACE endpoint (and all individual components) censoring rules updated.
3.1	Changed the calculation of patient's age to be from date of start of screening instead of date of informed consent.
3.2	Updated sub-level categories.
5	- Added PCSK9 inhibitors to the list of non-statins. - Added SGLT2 inhibitors to the list of other oral hypoglycemic agents. - Added rules for the summary of statin use for the determination of the daily dose for each patient.
6.3.2	- Updated the definition of new onset diabetes. - Updated the second set of criteria for determining new onset diabetes.
6.3.5.1	Clarified that comparisons will be between each treatment and placebo.
6.3.5.3	- Clarified that change from baseline will be summarized. - Clarified that comparisons will be between each treatment and placebo.
6.3.5.6	Corrected the % missing cut off from more than 50% to 50% or more.
7.3.1	Amended the cut off for common events from 1% to 2%.
7.3.3 (Table 7-2)	Amended clinically notable changes in vital signs criteria.
7.4	Inserted table 7-3 with an updated list of AEs of special interest.
7.4.2	- Clarified baseline glycemic and abnormal LFT subgroup analyses. - Updated the covariates in the ordinal regression.
7.4.3	Amended the identification of malignancy.
12	Added references.

Amendment 1, June 26, 2014

Section	Changes
2.2	Updates to the per-protocol analysis sets.
2.2	Updates to the subgroup definitions.
2.3.2	Clarification of the hsCRP the baseline value.
3	Minor updates and clarifications to patient disposition, demographics, and medical history.
6.1.1	New section 6.1.1 was added for endpoint adjudication process.
6.3.1	- Addition of an additional early futility analysis to be performed at approximately 30% of the target number of 1400 patients have experienced CEC confirmed MACE, as per protocol amendment 8. - Clarification that in case one active arm is stopped, the target number of patients with a MACE that is still to be collected has to be adjusted. For patients whose treatment arm is stopped per DMC recommendation, follow-up for cardiovascular (CV) and safety events will continue.

Section	Changes
	- A sensitivity analysis will be performed by performing the primary analysis excluding all patients who were unblinded during the double blind phase of the study. - Change from baseline to the last hsCRP prior to the 1st confirmed MACE will be summarized by treatment.
6.3.2	- Clarification added that all identified cases of new onset of diabetes will be confirmed by the adjudication committee. - Clarifications on subgroup analyses for the key secondary new onset of diabetes endpoint.
6.3.4	Updates and clarifications to exploratory analyses.
6.3.5	Updates to SIS-16 (sub-section 6.3.5.6).
7	Several minor updates and clarifications.
8	Protocol amendment 8 introduced an additional early futility analysis to be performed at approximately 30% of the target number of 1400 patients have experienced CEC confirmed MACE.
12	Added new reference.

1 Introduction

The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS; Novartis study code CACZ885M2301) is a randomized, double-blind, placebo-controlled, event-driven trial of quarterly subcutaneous canakinumab in the prevention of recurrent cardiovascular events among stable post-myocardial infarction patients with elevated hsCRP.

This document outlines the agreements for the Statistical Analysis Plan for CANTOS based on the discussions between Brigham and Women's hospital and Novartis. The detailed statistical analysis plan including additional supportive/exploratory analyses, table shells and data set specifications will be prepared on this basis.

It is planned that after the end of the core study visit patients will be followed for safety in an extension study. Data collected after the end of the core study visit will not be part of the main CANTOS clinical database and analyses using data from this extension study will not be specified in this document.

2 Definitions

2.1 Analysis sets

The following analysis sets will be defined for statistical analysis:

- **Screened set** – All patients who signed the informed consent.
- **Randomized set** – All patients who received a randomization number, regardless of receiving trial medication.
- **Safety set (SAF)** – All patients who received at least one dose of study drug and have at least one post-baseline safety assessment. Of note, the statement that a patient had no adverse events also constitutes a safety assessment. Patients will be analyzed according to treatment received. Treatment received will be considered identical to the randomized treatment if the patient has during at least one visit received the two injections constituting the treatment assignment at randomization.

  For patients who cannot be assigned in this manner, the most frequent dose at an individual visit (as defined in table 2-1) will be considered the treatment received. In the case of more than one equally frequent dose (ties), the highest most frequent dose will be assigned.

  Note: Any patient who did not receive any injection of study drug during the study is automatically excluded from the safety set, due to the lack of at least one dose of study medication.

Table 2-1 Definition of dose received at a visit

Sum of injection doses* [mg]	Dose at the visit
0 (meaning ≥ 1 placebo injections, but not even a partial canakinumab injection)	Placebo

Sum of injection doses* [mg]	Dose at the visit
> 0 to ≤ 50 mg of canakinumab	Canakinumab 50 mg
> 50 to ≤ 150 mg of canakinumab	Canakinumab 150 mg
> 150 of canakinumab	Canakinumab 300 mg

* Placebo injections counted as 0 mg

- **Full analysis set (FAS)** – All randomized patients. This is the primary efficacy population applied in all efficacy variables. Following the intent-to-treat principle, patients are analyzed according to the treatment they have been assigned to at the randomization. However, patients who have not been qualified for randomization and who have been inadvertently randomized into the study are excluded from FAS, provided these patients have not received study drug. (Note: The last part of the definition of the FAS is what is often referred to as misrandomized patients; i.e. patients for whom IVRS calls were made by the site either prematurely or inappropriately prior to confirmation of the patient's final randomization eligibility and double-blind medication was not administered to the patient. These patients would subsequently not continue to take part in the study or be followed-up. Misrandomized patients will not be included in the FAS, but they will be included in the Randomized Set. Further exclusions from the FAS may only be justified in exceptional circumstances; e.g., serious Good Clinical Practice violations).

  Per protocol set 1 (PPS1) – a subset of the FAS, consists of all randomized patients in FAS who take at least one dose of study medication and have no major protocol deviations affecting the primary analyses. Major protocol deviations leading to exclusion from PPS will be specified prior to database lock on a blinded basis and documented in a separate document. Data from patients discontinuing treatment will be censored a quarter year + 28 days after their last study drug injection.

All cases of prospectively defined protocol deviations will be identified prior to clinical database lock / unblinding and entered into a dedicated data panel as part of the locked database. Certain deviations may stipulate that only data up to the time of infraction will be included in the PP analysis, i.e. for analyses of the PP set data beyond this time-point will be ignored. This supplemental efficacy population is used to assess robustness of the primary analysis results. All exceptional cases and problems and the final decisions on the allocation of patients to populations will be fully defined and documented before data base lock (in particular before breaking the blind where applicable) and will be fully identified and summarized in the clinical study report as per the harmonized International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use tripartite guideline on statistical principles for clinical trials.

Criteria defining protocol deviations are provided in the Data Handling Plan (DHP). Protocol deviations will not lead to patient withdrawal from the study unless they indicate a significant risk to the patient's safety.

For the purpose of summarizing major protocol deviations, these will be considered to be those protocol deviations that lead to the exclusion from an analysis set. The current draft list of criteria leading to exclusions from analysis sets is shown in Table 2.2. Other currently

foreseen protocol deviations will be reported in the clinical study report, but these will not lead to an exclusion from any analysis set. It is not currently foreseen that any criteria would lead to an exclusion from PPS from date of deviation.

Table 2.2 Criteria leading to exclusions from analysis sets

Analysis set	Criteria that cause a screened patient to be excluded
Screened	none
Safety (SAF)	Patients not receiving any dose of double-blind study medication
Randomized	Patient without a randomization number
	Patient was not randomized but took study drug (covered by the above)
Full Analysis Set (FAS)	Patient mis-randomized
	Patient without a randomization number
	Patient was not randomized but took study drug
	Site closed for GCP non-compliance (data integrity was impacted)
Per Protocol set 1 (PPS1)	Patient mis-randomized
	Patient without a randomization number
	Patient was not randomized but took study drug
	Patients not receiving any dose of double-blind study medication
	Patient participates in any other investigational drug or device study or patient has received an investigational drug or device <= 30days of Visit 1 except for previous DES trial on countries with approved DES devices
	Patient received study drug, and was later discontinued due to not meeting the entry criteria
	Major surgical procedure including PCI or CABG performed during the study but planned prior to randomization.
	CABG < 3 years prior to visit 1
	Patient is currently (i.e. at randomization) taking a biological drug targeting the immune system (ie: TNF blockers, anakinra, rituximab, abatacept, tocilizumab)
	Documented MI does not meet entry criteria or Date of most recent MI = blank but there is a visit 2
	Screening hsCRP < 2 mg/L or = blank
	Qualifying hsCRP measurement date < 28 days after date of prior PCI or Qualifying hsCRP measurement date < 28 days after date of qualifying MI
Exclusion of data from PPS from date onwards	Data from patients discontinuing treatment will be censored a quarter year + 28 days after their last study drug injection.

2.2 Subgroup definitions

Generally subgroup analyses within a trial should be kept to a minimum. However, subgroup analyses need to be presented in submission documents like Summary of Clinical Efficacy, Summary of Clinical Safety, and Risk Management Plan and the clinical study report for the CANTOS trial will likely at least fulfill the first two of these roles.

The objective of the subgroup analyses is to evaluate the consistency of treatment effects across a wide variety of patient groups.

The primary composite (MACE) endpoint of CV death, nonfatal MI and nonfatal stroke, the key secondary variables and potentially other important efficacy variables will be analyzed for the subgroups shown in the Table 2.3-1.

Table 2.3-1 Subgroup analyses for the primary major adverse cardiovascular event (MACE) endpoint and other key efficacy outcomes

Subgroups	Definition
Age (at study start)	<65, ≥65 years ; <75, ≥75 years
Sex	male, female
Race	Asian, Black, Caucasian, Other
Ethnicity	Hispanic / Latino, Asian, Other, Unknown
Type of qualifying MI	STEMI, non-STEMI, unknown
BMI at baseline	< 25, ≥ 25 & < 30, ≥ 30 kg/m^2 ; < 35, ≥ 35 kg/m^2
Region	• Asia: China, India, Japan, South Korea, Taiwan • Western Europe: Austria, Belgium, Germany, Greece, Iceland, Italy, Netherlands, Norway, Sweden, United Kingdom • Central Europe: Bulgaria, Croatia, Czech Republic, Estonia, , Hungary, Latvia, Lithuania, Poland, Romania, Russian Federation, Serbia, Slovakia, Slovenia, Turkey • Latin America: Argentina, Brazil, Colombia, Guatemala, Mexico, Peru • North America: Canada, United States • Others: Australia, South Africa In addition to the above regions in all tables by region subgroup, an analysis for Japan (and Japan plus Korea) will also be presented separate regardless the size of enrollment in these countries to meet Japanese regulatory requests.
Glycemic status at baseline	Normoglycemic, pre-diabetic, diabetic Pre-diabetic is defined by one of the followings • HbA1c ≥5.7% & <6.5% • FPG ≥100 & <126 mg/dl • FPG ≥ 126 mg/dl at either Visit 1 or Visit 2 (or any unscheduled visit between, but only occurring on one visit) • HbA1c ≥ 6.5% at either Visit 1 or Visit 2 (or any unscheduled visit between, but only occurring on one visit) Diabetic is defined by one of the followings • FPG ≥ 126 mg/dl at Visit 1 and Visit 2 (or any unscheduled visit between)

Subgroups	Definition
	• HbA1c ≥ 6.5% at Visit 1 and Visit 2 (or any unscheduled visit between) • Combination of FPG ≥ 126 mg/dl and HbA1c ≥ 6.5% as confirmed at Visit 1 and Visit 2 (or any unscheduled visit between) • Medical history of Type I or Type II diabetes mellitus • Anti-diabetic medication use
Smoking status at baseline	Never, current, former
Baseline hsCRP level	≤ 4, > 4 mg/L
Baseline LDL-C level	< 70 mg/dL, >= 70 mg/dL; Tertiles of baseline LDL-C (This will be done using the calculated LDL-C unless triglycerides > 400 mg/dL in which case a direct (i.e. measured) LDL-C will be used)
Baseline SBP level	< 130 mmHg, ≥ 130 mmHg
Baseline DBP level	< 80 mmHg, ≥ 80 mmHg
Baseline statin dose level	No, low, moderate, and high
Baseline aspirin usage/dose	Yes / No
Medical history of gout	Yes / No
Cardiovascular risk factors	
Hypertension	Yes / No
Dyslipidemia	Yes / No
Prior PCI	Yes / No
Prior CABG	Yes / No
Prior TIA/stroke	Yes / No
History of heart failure	Chronic Heart Failure occurrence (yes/no)
eGFR MDRD	< 60, ≥ 60 & < 90, ≥ 90 mL/min/1.73m^2
Time since index MI	< 6 vs. ≥ 6 months ; < 12 vs. ≥ 12 months
Presence of MI prior to index MI	Yes / No

A set of standard safety subgroups shown in Table 2.3-2 will by default be looked at for selected safety analyses (see section 7).

Table 2.3-2 Standard safety subgroups

Subgroup	Definition
Age	<65, ≥65 years; <75, ≥75 years
Sex	male, female

Subgroup	Definition
Race	The same as above
Ethnicity	The same as above
Region	The same as above
Time since index MI	< 6 months vs. ≥ 6 months
BMI	The same as above
Medical history of gout	Yes / No
Co-existing medical conditions of interest: T2DM	Yes / No
Baseline hsCRP level	The same as above

In addition to the two preceding sets of subgroups those specified in Table 2.3-3 will be used in some analyses as stated in the relevant analysis plan sections. They are shown here irrespective of what kind of analysis they will be used for to highlight that they needed to be included in analysis datasets.

Table 2.3-3 Additional subgroups needed only for specific analyses

Subgroups	
Duration of diabetes	< 3, ≥ 3 & < 10, ≥ 10 years
Basis for diabetes diagnosis	• Medical History of Type I or Type II diabetes mellitus • Medical History and Anti-diabetic medication • Medical History and Baseline HbA1c/FPG • Medical History and Anti-diabetic medication and Baseline HbA1c/FPG • Anti-diabetic medication • Anti-diabetic medication and Baseline HbA1c/FPG • Baseline HbA1c/FPG
Baseline HbA1c categories	• HbA1c < 7% at randomization for deterioration of glycemic control analyses (HbA1c ≥ 7.5% at 6 month visit or beyond, confirmed by a second/unscheduled HbA1c measurement within 6 weeks) [i.e. Among those randomization diabetic patients, we look at the sub-group of patients with HbA1c < 7% at visit 2. Then we would analyze how many of those patients experience a deterioration of glycemic control as documented by an increase of HbA1c to >= 7.5% at 6 months or beyond, confirmed within 6 weeks.] • For HbA1c benefit analysis in diabetics (HbA1c < 8%, ≥ 8%) [i.e. analysis of mean HbA1c change from baseline in T2D patients with baseline HbA1c < 8% and >= 8%.]
History of macular degeneration	Medical history or use of relevant medications
Baseline neutrophil levels	Abs neutrophils < 1.5 , ≥ 1.5 x 10^9 /L .
Baseline use of antithrombotic medications	Yes/No
key drugs for the trial population affected by CYP450 with a narrow therapeutic index (e.g. warfarin and amiodarone)	Yes/No •
Vaccines	Yes/No
Medical history of gout, rheumatoid arthritis or other inflammatory diseases such as lupus or psoriatic arthritis	Yes/No
History of malignancy	Yes/No - Yes will correspond to patients with SMQ “Malignant or unspecified tumors” in Medical history
Baseline QTcF	Elevated or normal

Subgroups	
	Normal • ≤ 430 msec for men, ≤ 450 msec for women Elevated • > 430 msec for men, > 450 msec for women.
Baseline heart rate	< 55 bpm versus ≥ 55 bpm
Alcohol history	Yes / No
Baseline platelet counts	< 150, ≥ 150 x 10^9 /L
Early drops in platelet counts (or thrombocytopenia) Ordinal	< 25, ≥ 25 - <50, ≥ 50 - <75, ≥ 75 - < LLN, >=LLN at visit 3. Repeat at visit 4;
Early drops in platelet counts (or thrombocytopenia) defined by % change from baseline	< 20% and ≥ 20% drop from baseline to visit 3. Repeat at visit 4
Early drops in neutrophils (or neutropenia)	<0.5, ≥0.5 - <1.0, ≥1.0 - <1.5, ≥1.5 - <LLN at visit 3. Repeat at visit 4
Early drops in neutrophils (or neutropenia) defined by % change from baseline	< 20% and ≥ 20% drop from baseline to visit 3. Repeat at visit 4
baseline neutropenia	CTC >=3 (yes/no)

To support regional submission activities and health authority interactions, at a minimum the subgroups shown in table 2.3-4 are needed.

Table 2.3-4 Regional/country subgroups to support regional/local submissions, for which selected tables have to be repeated

Preliminary* list of variable(s) / analyses to be repeated	Regional/country subgroup
On FAS Disposition/Demography/Patient and disease characteristics Incidence of primary endpoint Incidence of key secondary endpoints Incidence of secondary endpoints (includes death) Analyses of other selected efficacy variables (e.g. hsCRP) Medical environment (e.g. prior/concomitant medications including statin dose, revascularization/stenting/etc. for index MI) PK and PD (especially hsCRP) **On SAF** Adverse events by system organ class and preferred term Serious adverse events by system organ class and preferred term Deaths Standardized MedDRA queries	1. Japan 2. Japan and Korea 3. Mainland China 4. Mainland China + Taiwan 5. Asian patients: Japan, China, Taiwan, and Korea 6. India 7. Russia

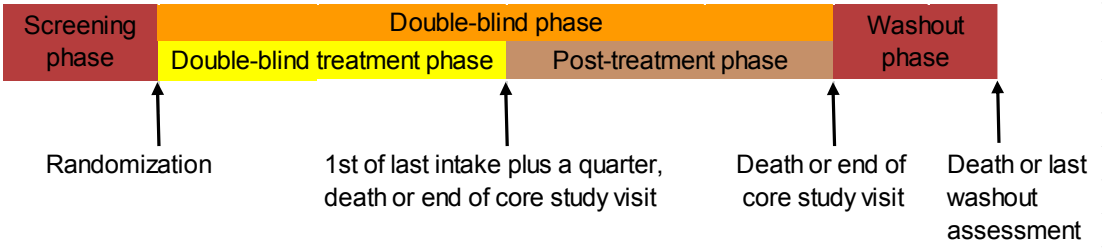
Preliminary* list of variable(s) / analyses to be repeated	Regional/country subgroup
Adverse events of special interest	

* subject to changes dependent on local requirements

2.3 Assessment windows, baseline and post baseline definitions, missing data handling

2.3.1 Assessment windows and visit mapping

Figure 2-1 Assessment windows



Screening phase

The screening phase is defined as the period prior and up to randomization. After obtaining written informed consent, the patient will be evaluated for eligibility to participate in to the study.

Double-blind phase

The double-blind phase includes double-blind treatment phase and post-treatment phase. It does not include the washout phase or any long-term follow-up after the completion of this trial. The double-blind phase defined here is the same as the double-blind treatment period defined in the study protocol.

Double-blind treatment phase

The double-blind treatment phase refers to the time period during which patients actually receive treatment (or are still expected to have significant PK exposure).

The double-blind treatment phase begins at the time of randomization and ends with the earliest of the last trial drug intake plus a quarter year (91 days), the death of the patient or the last study assessment in the main part of the trial (i.e. excluding the washout). During the double-blind treatment phase, patients will return for scheduled clinic visits.

Post-treatment phase

The post-treatment phase refers to the time period during which patients no longer receive treatment and no longer have significant PK exposure up to the end of the study visit for the

core study. As this is an outcome study, patients should nevertheless be followed-up during this phase until the end of the core study, in order to assess the occurrence of trial endpoints.

The post-treatment phase (after unscheduled drug discontinuation or study completion/termination) begins after last study drug intake plus a quarter year (91 days) + 1 day and ends with the date of the end of core study visit or the death of the patient. During the post-treatment phase, patients should also continue to return for scheduled clinic visits.

The distinction between double-blind treatment phase and post-treatment phase does not affect the primary intention-to-treat analysis, but affects e.g. the supportive on-treatment sensitivity analysis.

2.3.2 Baseline definition

Baseline is defined as the last available measurement during the screening phase, i.e. prior and up to randomization. That means that if the measurement at the baseline visit is missing, then the previous measurement preceding baseline will be used as the baseline measurement.

For hsCRP the baseline value will be the mean of the available hsCRP values within 60 days prior and up to randomization.

2.3.3 Post-baseline definition

Post-baseline is defined as any assessment after randomization including treatments and outcomes that occur after but on the same day as randomization. On the other hand, measurements and laboratory samples taken on the day of randomization during the randomization visit (at the end of which a patient is randomized) are considered baseline assessments.

2.3.4 On treatment definition

As baseline is relative to randomization, it is necessary to confirm where events/assessments occur relative to intake of dose. Any event/assessment occurring on or after the time of the first intake of IP and up to 119 days after the last treatment intake for those patients who discontinued treatment will be deemed to have occurred whilst “on treatment”.

Scheduled Assessments: For scheduled assessments, both date and time are expected to be recorded in the database. However in the instance that only the date is recorded for an assessment, then the assessment will be deemed to have occurred prior to treatment. This is justified as protocol indicates injections will be given after all other study assessments have been completed for each visit.

Events: Should an event occur on the same day as first intake of IP, then the most conservative approach is to consider this to be on treatment.

2.3.5 Visit mapping for the study completion visit

As the core study completion visit will occur after a different length of follow-up for different patients, it needs to be defined for which scheduled timepoint assessments at the study completion visit are counted. I.e. it needs to be defined when e.g. plotting the quarterly/bi-

yearly hsCRP values over time, whether the study completion hsCRP should count for the 0.25 year visit, the 0.5 year visit, the 0.75 year visit, the 1 year visit etc., which will be based on when it occurred.

When showing values over time, study completion visit assessments will be displayed as if they had occurred at the next scheduled timepoint for that assessment. For example, if a patient has a regular month 45 visit and then the study completion visit occurs 2 months later, then the study completion visit would be considered to provide the patient's values for month 48.

2.3.6 Data from unplanned visits and unscheduled visits

Data from unplanned visits and unscheduled visits will not be re-mapped to other visits for the purpose of displaying variables over time except for laboratory data. For laboratory data, a time window will be used to identify the assessment closest to the target day within the window over time. The unplanned and unscheduled visits will be used in the analysis of event endpoints (e.g. new onset diabetes), and will be counted towards shift tables or other analyses regarding the worst observed values for patients.

Table 2-4 Time windows for endpoints based on HbA1c, FPG, standard hematology, biochemistry or fasting lipid profile

Time window	Start of time window (study days)	End of time window (study days)
Week 2 visit	1, but only after the laboratory assessment of the baseline visit	28
Month 1.5 visit	29	68
Month 3 visit	69	137
Month 6 visit	138	228
Month 9 visit	229	320
Month 12 visit	321	457
Month X visit (where X≥18 is a multiple of 6)	Rounded [(365.25 / 12) * (X – 3)] + 1	Rounded [(365.25 / 12) * (X + 3)]

Table 2-5 Time windows for urinalysis based endpoints

Time window	Start of time window (study days)	End of time window (study days)
Month 3 visit	1, but only after the laboratory assessment of the baseline visit	228
Month 12 visit	229	639
Month 30 visit	640	1096
Month 42 visit	1097	1461
Month X visit (where X≥42 is a multiple of 12 added to 30)	Rounded [(365.25 / 12) * (X – 6)] + 1	Rounded [(365.25 / 12) * (X + 6)]

2.3.7 Time window for post stroke assessments

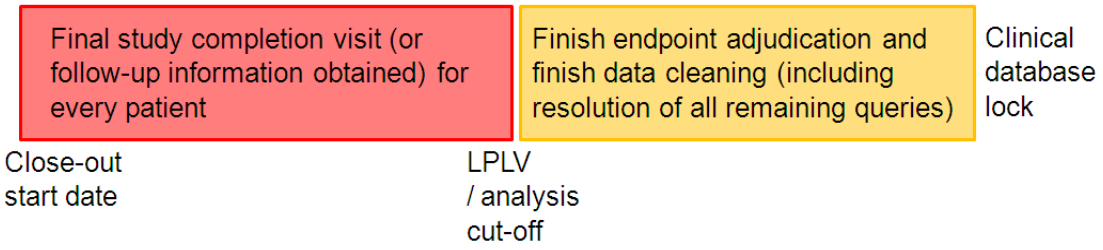
The three questionnaires (Modified Rankin Scale, Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF) and Stroke Impact Scale 16 (SIS-16)) are planned to be administered 30 days and 90 days after a patient has a stroke. The actual number of days between the patient's last stroke and the date of the assessment will be derived as (Date of last stroke – Date of questionnaire assessment + 1). The date of last stroke will be derived using both investigator and adjudicated data to find the last stroke before the assessment (a patient could have multiple strokes during the study). The timepoints for analysis will be derived as follows:

- actual days since last stroke <60, then timepoint "30 days" will be assigned
- actual days since last stroke >=60, then timepoint "90 days" will be assigned

2.3.8 Close-out procedure

CANTOS is designed as an event driven trial with the aim to finish the core study when approximately 1,400 patients had a confirmed primary endpoint. A close-out procedure will be initiated with a timing appropriate to achieve this.

Figure 2-2 Overview of close-out procedure



The aim of the close-out procedure will be to allow for the execution of all necessary activities including the core study completion visits, data cleaning, raising and resolution of all queries to the clinical sites, and endpoint adjudication for endpoints that occurred during the core study and prior to final visit/analysis cut-off, whichever occurs first.

The close-out procedure will start based on the estimated date when the confirmed target number of events will be reached, with final patient visits occurring until the date of the last visit of the last patient (LPLV), and finish with the clinical database lock. The analysis cutoff date will be defined as the LPLV.

It will be attempted to follow each patient until a final study completion visit between the close-out start date and the analysis cut-off date unless the patient died. If a patient does not attend the final visit in person, there will be attempts to obtain information by other means between the close-out start date and the analysis cut-off date; this information will be available under the final study completion visit.

For patients who withdrew consent, the follow-up information such as vital status and whether endpoints occurred ("yes", "no", "unknown") will still be collected during the close-out period to the maximum extent possible under local regulations.

Events occurring after the final visit, but before the analysis cut-off for patients that entered the long-term follow-up or the washout, will not be entered as endpoints into the database for the main trial.

2.3.9 Missing data handling

Imputation of missing date

As a general approach each time it is appropriate the partially missing date reported as character date in the data will be imputed.

- If only the month is known, then the 15th day of this month will be imputed.
- If only the year is known, then the 1st July will be imputed.

As a general approach no imputation will be performed on completely missing date.

For AEs specific rules to impute partially missing start/end dates are defined in the ADAM specification.

For prior and concomitant medications specific rules to impute partially missing dates are defined in the ADAM specification.

Time-to-event variables

Regarding time-to-event variables only observed/reported events will be used in the analysis – i.e. events will not be imputed for censored patients, except for specific sensitivity analyses. This means that in the primary analysis censoring of non-observed events will be assumed to be non-informative. Incomplete dates of events and censoring dates will be imputed as described below.

In the primary analysis, all patients, including those who discontinue study therapy due to lack of efficacy, adverse events or abnormal laboratory values, will be followed until death or the end of the study. Information on patients discontinuing study drug or participation in trial visits will be collected whenever possible and will be used in the analysis.

In general, every effort will be made to collect information about the primary outcome events for those patients who discontinued treatment or their participation in the trial. In patients who could not be followed up for primary outcome events, it is aimed to at least determine the vital status of the patients at the final visit.

The following rules will be applied separately for the composite MACE endpoint and for all its individual components. Patients who have not experienced the respective endpoint will be censored on the date of the last follow-up defined as the earliest of:

- the date of death unless the patient withdrew his consent for the collection of follow-up information,
- the date of the last visit satisfying at least one of the following:
  - yes to the question of "indicates if the subject attended the scheduled visit" on the Visit Information CRF
  - yes/no to the question of "any clinical events since last visit" on the Visit Information CRF

- yes/no to the top three questions (death, myocardial infarction, stroke) on the Clinical Event Tracking CRF.

Should the censoring date lie after the chosen analysis cut-off date, it will be set to the analysis cut-off date. Note that this censoring date should be derived independently of any specific analysis other than all cause mortality, because it will be used to describe the extent of follow-up for (potentially multiple) cardiovascular events and for multiple different time-to-event analyses (e.g. time to MACE, time to MI, analyses of multiple cardiovascular events). For all-cause death, the censoring will occur at the minimum of withdrawal of consent, last known alive date and analysis cut-off date.

If the date of a MACE endpoint or of censoring is not known or is incomplete following all attempts to get an approximate date, a day will be imputed using the following algorithm:

- If only the month of the event is known, then the 15th day of this month will be imputed.
- If only the year of the event is known, then the 1st July will be imputed.
- If year, month and day are unknown, the event date will be imputed as the randomization date and the patient will be assumed to have had a MACE event post-randomization on day 1 of the follow-up.
- If this imputation rule leads to a date before the randomization date or after a patient's last study visit or after a patient's death, but the date could have been on one of these dates, then the event date will be imputed to be the one out of these dates that the incomplete date is consistent with.
- In the first three bullet points it will also be taken into account, whether it is known that a patient was event free up to a certain time. If that is the case the imputed date will be restricted to be after the date up to which the patient was event free, unless this is incompatible with the incomplete date or violates the 4th bullet point.

Date of trial drug injection

In case of missing information on the day of injection of any study medication the date of the corresponding dispensing visit will be used as date of injection. If that is missing the date foreseen for that visit in the protocol will be assumed.

Other missing data

Missing laboratory, vital signs, ECG, quality of life and other data will not be imputed for the purpose of summary statistics. Such summary statistics will be displayed longitudinally showing only those values that are available. Subsequent more in-depth analyses may explore other approaches and appropriate data imputation methods will be chosen for each type of analysis.

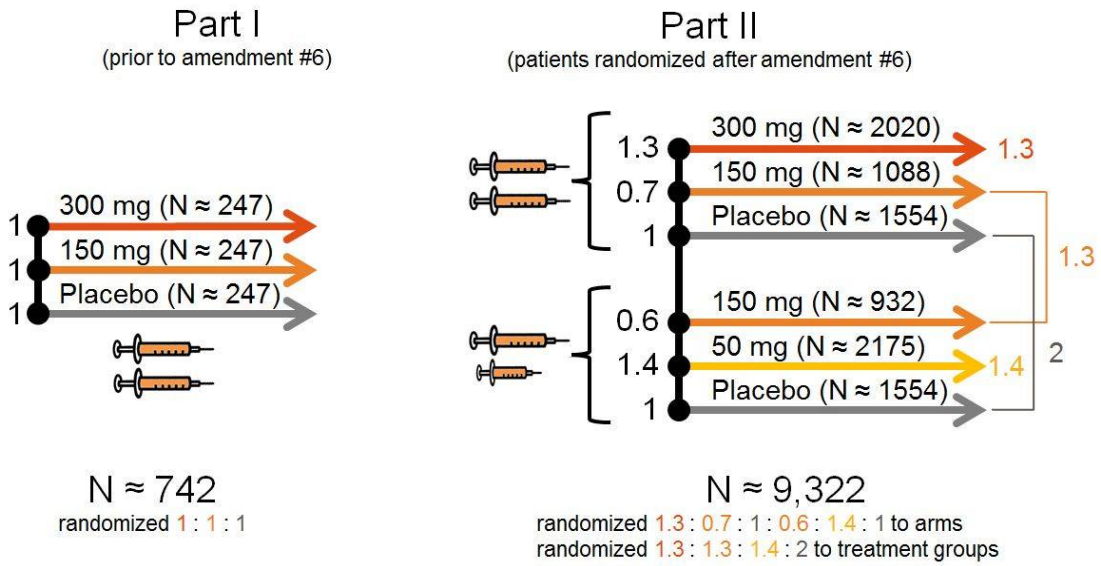
2.4 Key trial design aspects relevant to trial analysis

Randomization and blinding

Initially, patients were randomized in a 1:1:1 fashion to 300 mg canakinumab with induction dose, 150 mg without an induction dose or placebo quarterly. Following Health Authority feedback on the doses a lower 50 mg dose arm was added in protocol amendment 6 in order to

examine the dose response of canakinumab in preventing recurrent cardiovascular events, and to determine if a dose lower than 150 mg would have a favorable risk benefit ratio. Following this amendment, randomized allocation to the four trial arms was to be unbalanced in order to optimize power, now that three active arms were compared versus a common control arm.

Figure 2-3 Patient allocation to treatment arms prior and after protocol amendment 6 including reduced patient numbers following protocol amendment 8



Protocol amendment 6 introduced 50 mg dose. In protocol amendment 8, the total sample size was changed from 17,200 to10,000. The allocation to active drug is always 2:1 (in Part I, Part IIA and IIB).

Prior to protocol amendment 6, the following two presentations of canakinumab solution for injection in pre-filled syringes are used in CANTOS:

- Canakinumab 150 mg/1 ml, and
- Placebo matching canakinumab 150 mg/1 ml

In addition, the following pre-filled syringes were available to be used for the purpose of implementing the 50 mg arm following amendment 6:

- Canakinumab 50 mg/0.5 ml, and
- Placebo matching canakinumab 50 mg/0.5 ml.

Canakinumab 50 mg/1 ml pre-filled syringes that fully match 150 mg pre-filled syringes were not available near the time of protocol amendment 6. Thus, in order to evaluate 300 mg, 150 mg and 50 mg versus placebo in a fully blinded fashion, a triple-dummy design with 3 injections per visit would have been required. As feedback from investigators indicated that this would constitute an unacceptable burden to patients we identified the approach shown in Figure 2-3 as the most appropriate solution for introducing the 50 mg dose into the CANTOS trial.

For the three trial arms in Randomization Plan A, study drug will consist of two injections of canakinumab 150 mg/1 ml or the matching placebo, while the three trial arms in Randomization Plan B study drug will consist of one injection of canakinumab 150 mg/1 ml, or the matching placebo and one injection of canakinumab 50 mg/0.5 ml, or the matching placebo. While investigators will be able to deduce from the size of the pre-filled syringes whether a patient is in Randomization Plan A or B, the chance that the patient is on active treatment is the same in either case (2:1). I.e. they are fully blinded with respect to active treatment or placebo, but can rule out one of the three possible active doses in case the patient was to be on active treatment.

As a result, the pre-specified primary analysis described in detail in section 6.3 comprises both

1. a randomized contrast between groups that are completely double-blind versus each other (canakinumab 150 mg versus placebo) and veiled versus the other groups and
2. two randomized contrasts between groups that are veiled (canakinumab 300 mg versus placebo and 50 mg versus placebo).

The term veiled is used in the sense of Senn (Senn 1995), who defines a veiled trial as a trial in which a patient's treatment group is not known, but the possibilities can be narrowed down to a subset of all existing treatment groups in the trial - in CANTOS every patient can clearly only be in 3 out of the 4 trial arms, either a patient can be on canakinumab 300 mg, 150 mg, or placebo or the patient can be on canakinumab 150 mg, 50 mg or placebo.

As far as combining data from trial part 1 and trial part 2 is concerned, the pre-specified analysis preserves the double-blind nature of the contrast in the same way that a patient-level (network) meta-analysis would. This is done by not making any direct comparisons between patients in trial part 2 and those in trial part 1 - i.e. no naïve pooling of patients across trial part, which would have been inappropriate, because patients were not concurrently recruited for the two trial parts and assignment to trial part was not at random. Instead, for example the 50 mg dose in trial part 2 can only be compared to the placebo group in trial part 1 indirectly using a double contrast by combining the 50 mg versus 300 mg and 50 mg versus 150 mg contrasts in trial part 2 with the 300 mg versus placebo and 150 mg versus placebo contrasts in trial part 1. As discussed by Senn, estimates obtained in this way have a substantially higher variance than the direct single (potentially biased) contrast (Senn 2008). Comparisons between treatments randomized to Part II on the other hand pool all concomitantly randomized arms because the potential bias is considered to be too small to justify the loss in efficiency incurred by such an approach. Furthermore, it was decided that any hypothetical bias could be handled for several reasons. Firstly, because patients are randomly assigned to the two randomization plans, one can expect patients in randomization plan A and B to be comparable at baseline. Secondly, any possible bias is expected to be small, if it exists. While investigators and patients can potentially identify whether patients are either on 300 mg, 150 mg, or placebo (trial part 1 or randomization plan A in trial part 2) or alternatively on 150 mg, 50 mg, or placebo (randomization plan B in trial part 2), the odds of a patient being on active treatment are the same in either case (2:1). In either case the number of potential treatment groups is only narrowed down to a limited extent, namely from 4 to 3. Taken together, this makes it unlikely that any influence of this knowledge on investigators and patients would have any substantial impact with respect to e.g. patient management, follow-up or endpoint

reporting. Thirdly, whether this is the case can be confirmed at the end of the trial due to the presence of both a placebo arm and a 150 mg arm in both randomization plans. For this purpose the placebo groups in randomization plans A and B will be compared against each other for the primary MACE endpoint, the 150 mg groups in randomization plan A and B will be compared and the 150 mg versus placebo contrasts will be compared between randomization plan A and B.

3 Patient disposition, background and demographic characteristics

3.1 Patient disposition

The number of patients screened, randomized and included in the full analysis set (FAS), the per protocol set 1 (PPS1), and the safety set will be presented by treatment group and overall for the screened set, as well as by trial part. For the screened set the reasons for screen failures will be tabulated. The number and percentage of patients in the randomized set who completed the study, who discontinued the study (lost to follow-up, patient/guardian decision, technical problems, death), the reason for discontinuation of study medication, and vital status (known vs unknown for lost to follow-up and patient/guardian decision) will be presented for each treatment group and all patients, as well as by trial part. Some patients may have multiple visits where drug is not administered prior to permanent discontinuation. Each visit may have a different reason for not administering drug. For these cases, the following hierarchy will be used to assign the most conservative reason for permanent discontinuation of study medication:

- If a patient has at least one AE with an outcome/ action reported as permanent treatment discontinuation, then AE will be the reason
- If the scenario in bullet 1 did not occur and there is at least one reason on the Dosage Administration Record CRF that states the reason for not administering study medication is “ADVERSE EVENT”, then AE will be the reason
- If the scenarios in bullets 1 and 2 did not occur, the reason associated with the last visit the patient actually came into the clinic will be used as the reason for permanent discontinuation of study medication if the patient did not receive study medication at that last in-clinic visit. If the patient did receive study drug at the last in-clinic visit, the reason for not administering study drug associated with the first visit that the patient did not come into the clinic will be used as the reason for permanent discontinuation of study medication.

The frequency (%) of patients with protocol deviations as well as the criteria leading to exclusions from analysis sets will be presented in separate tables for the randomized set. Finally, the number of enrolled and randomized patients by region (see section 2.2) as well as the number of patients enrolled and randomized per region and country will be presented descriptively for the randomized set overall and by trial part.

When the exact date of birth cannot be collected for data privacy reasons, the year of birth is collected instead and the patient’s age is imputed by the Oracle Clinical Remote Data Capture system (OC/RDC) on that basis. For that purpose OC/RDC assumes the patient’s birthday to

have been on 1 July of the year and calculates the patient's age as the number of days between that day and the date of the start of screening divided by 365.25.

3.2 Background and demographic characteristics

The common background and demographic variables will be summarized by treatment and the total of all patients using descriptive summary statistics (for continuous variables mean, median, standard deviation, Q1 (25th percentile), Q3 (75th percentile), minimum and maximum and for categorical variables frequency and percentage).

Summary of baseline demographic characteristics will include:

- Age [years]; age categories <65, ≥65 to <75, ≥75 years
- Sex (male/female)
- Race (Caucasian, Black, Asian, Native American, Pacific Islander, Unknown, Other) and Ethnicity (Hispanic, East Asian, Southeast Asian, South Asian, West Asian, Russian, Mixed ethnicity, Not reported, Unknown, Other)
- Height [cm]
- Weight [kg]
- Body mass index [kg/m^2] calculated as weight [kg]/ $height^2$ [m^2]; BMI categories of <25, ≥25 to <30, ≥30 to <35, ≥35 kg/m^2
- Waist circumference [cm]

Summary of baseline risk characteristics will include:

- Sitting pulse [bpm]
- Mean sitting SBP [mmHg]; additionally tertiles and categorization of < 130 vs. ≥ 130 mmHg
- Mean sitting DBP [mmHg]; additionally tertiles and categorization of < 80 vs. ≥ 80 mmHg
- Controlled baseline blood pressure (msSBP < 130 mmHg and msDBP < 80 mmHg)
- Smoking history (Never/Current/Former)
- Alcohol history (amount consumed on average per day <1, 1 to 2, >2 to 3, >3 to 4, >4 to 5, >5 or more)
- Cardiovascular risk factors and other co-morbidities (as per protocol solicited events CRF, unless otherwise specified):
    - Glycemic status (T2DM, T1DM, pre-diabetes, normoglycemic; MedDRA terms to identify T1DM will be pre-specified)
    - Complications of diabetes
        - Family history of diabetes
        - Diabetic retinopathy (Diabetic proliferative retinopathy/Diabetic non-proliferative retinopathy)
        - Diabetic nephropathy
        - Diabetic neuropathy
        - Diabetic foot ulcers

- Hypertension
- Dyslipidemia/Hyperlipidemia
- Prior TIA/stroke
  - Prior Transient Ischemic Attack
  - Prior Hemorrhagic Stroke
  - Prior Ischemic Stroke
  - Prior Stroke of unknown type
- Atrial fibrillation
- Supraventricular tachycardia
- Deep Vein Thrombosis
- Pulmonary embolism
- Peripheral Arterial Disease
- Prior repeated MI (multiple MIs identified via narrow Myocardial infarction SMQ in medical history)
- Prior coronary revascularization
  - Prior PCI (from the Prior Coronary Revascularization Procedures CRF)
    - For the qualifying MI
    - Not for the qualifying MI
  - Prior stent implantation (incl. drug eluding stent or bare metal stent; from the Prior Coronary Revascularization Procedures CRF)
  - Prior CABG (from the Prior Coronary Revascularization Procedures CRF)
    - For the qualifying MI
    - Not for the qualifying MI
- Heart failure (identified in Medical History using narrow Cardiac Failure SMQ)

- Medical history of gout (as per protocol solicited events CRF)
- Medical history of macular degeneration (list of MedDRA terms to be pre-specified)
- Time since index MI: summary statistics and classification into
  - < 6 months post-index MI sub-classified into
    - <30 days,
    - 30 days to 3 months (≤91 days)
    - 3 months (>91 days) to 6 months (<183 days)
  - ≥ 6 months post-index MI sub-classified into
    - 6 months (≥183 days) to 1 year (≤365 days)
    - 1 year (> 365 days) to 2 year (≤731 days)
    - 2 (>731 days) to 3 years (≤1096 days)
    - 3 (>1096 days) to 5 years (≤1826 days)
    - 5 (>1826 days) to 7 years (≤2557 days)
    - 7 (>2557 days) to 10 years (3653 days)

  - > 10 years (>3653 days)
- Type of qualifying MI (stemi, non-stemi, unknown)
- Type of diagnosis for qualifying MI (ECG, Elevated cardiac markers, Both, cardiac imaging)
- Number of prior MIs; number of prior MIs categorization as 0, 1, 2, 3, and ≥4
- hsCRP [mg/L]; tertiles, categories <3 mg/L, 3 to < 4 mg/L, ..., 9 to < 10 mg/L, ≥ 10 mg/L
- HbA1c [%]; categories <5.7%, ≥5.7 – <6.5%, ≥6.5 to <7.5%, ≥ 7.5% (overall and by each glycemic status)
- FPG [mg/dL]; categories <100 mg/dL, ≥100 to < 126 mg/dL, ≥126 to < 200 mg/dL, and ≥200 mg/dL (overall and by each glycemic status)
- Total cholesterol [mg/dL]; total cholesterol tertiles
- LDL-C mg/dL, LDL-C tertiles, LDL-C categories <70 mg/dL vs. ≥ 70 mg/dL, LDL-C < 100 mg/dL vs. ≥100 mg/dL.
- HDL-C mg/dL, HDL-C categories (<50 vs. ≥50 mg/dL for female; <40 vs. ≥40mg/dL for male)
- Triglycerides mg/dL; triglycerides tertiles; triglycerides categories < 150 vs. ≥ 150 mg/dL
- eGFR [mL/min/1.73m^2]; categories < 30, ≥30 to <60, ≥60 to <90 and ≥90 mL/min/1.73m^2
- Level of exercise (rarely/never, less than once a week, once a week, 2-3 times a week, 4-6 times a week, daily)
- Family history of MI, stroke, diabetes or premature coronary artery disease (No / Yes with sub-categorization by age at first event)
- Highest level of education (0 years, 1-4 years, 5-8 years, 9-12 years, 13-16 years, >16 years)

For purely descriptive purposes, treatment group comparability will be examined using the Cochran-Mantel-Haenszel test stratified by time since index MI (< vs. ≥ 6 months) and trial part for the categorical variables and the F-test with time since index MI (< vs. ≥ 6 months) and trial part as a categorical covariate for the continuous variables as appropriate. These p-values will be provided for descriptive purposes and will not be considered to define any formal basis for determining factors that should be included in statistical models. Any concerns about imbalances between treatment groups are already addressed by the pre-specified sensitivity analyses that assess the treatment effects adjusted for pre-specified potentially prognostic covariates (see Section 6.3).

The eGFR is calculated using the MDRD formula. eGFR [mL/min/1.73 m^2]=175 × (serum Creatinine [umol/L]/88.4)$^{-1.154}$ × (age [years])$^{-0.203}$ × (0.742 if female) × (1.212 if African American) (Levey et al. 2007).

3.3 Medical History

Any condition entered on the *relevant medical history / current medical conditions* CRF will be coded using the MedDRA dictionary. Frequency tables will be provided by primary system organ class, preferred term and treatment group.

Adverse events occurring between screening and baseline will also be reported as medical history, but additionally reported separately as adverse events occurring between screening and baseline.

4 Study medication

The duration of the double-blind treatment phase will be computed as the time from the first injection to the first out of

1. the last injection date plus a quarter year (91 days),
2. the patient's death
3. the patient's study completion visit during the study close-out period
4. or the analysis cut-off.

This algorithm reflects the planned treatment schedule and the long half-life of the study drug. Missing dates in this algorithm will be imputed in the same way as missing dates for time-to-event analyses.

The duration of the post-treatment phase will be computed as the number of days from the day after the end of the double-blind treatment phase to the end of the post-treatment phase. If the end of the double-blind treatment phase coincides with the end of the double-blind phase, then the duration of the post-treatment phase will be 0 days.

The duration of the double-blind phase and double-blind treatment phase will be summarized for the FAS and SAF by treatment group descriptively including by duration categories. Overall patient-years will also be displayed and will be computed as the sum of patient days for all patients divided by 365.25.The duration of treatment, and of exposure will be summarized for the SAF by treatment group descriptively including by duration categories. Overall patient-years of treatment will also be displayed and will be computed as the sum of patient days of treatment for all patients divided by 365.25.

Duration of exposure to study treatment excluding interruptions will be computed and summarized as above for the SAF, but not counting periods during which the last injection was more than a quarter year ago. Duration of exposure will also be summarized for patients who are alive at the end of the study.

An interruption is defined as the period of time in which IP is deemed to be inactive. In other words, if the date of the last dose + 91 days, falls prior to the following dosing date, then the difference between these is equivalent to the interruption duration. It should be noted that a single interruption may span multiple scheduled administrations of IP.

5 Concomitant medication

Prior or concomitant medications will be summarized for the safety set in separate tabulations based on the coding dictionary used. Medications will be presented in order of descending frequencies, by preferred terms and grouped by anatomical main group. Tables will show the overall number and percent of patients receiving at least one drug of a particular preferred term and at least one drug in a particular anatomical main group.

Prior medications and significant non-drug therapies are defined as any medications and significant non-drug therapies taken prior to the start of study drug. Concomitant medications and significant non-drug therapies are defined as those used during the double-blind phase. Concomitant medications that were prohibited as per protocol and given during the conduct of the study as well as significant non-drug therapies will be summarized.

Furthermore, classes of medications to be precisely defined in a separate Excel file that will be stored in the Novartis CREDI system, will be summarized separately. These will include classes such as the following:

- Anti-ischemic agents
  - Beta blockers
  - Cardiac glycosides
  - Intravenous or oral nitrates
  - Calcium channel blockers
- Antithrombotic agents (excluding antithrombotic intravenous and subcutaneous drugs intended for acute setting such as abciximab, eptifibatide, or tirofiban, which are not expected to be used chronically and are consequently less relevant in this population – these will be reported separately in the Clinical Study Report)
  - Acetylsalicylic acid (aspirin)
  - Non-aspirin oral anti-platelet agents
    - P2Y12 inhibitors (like clopidogrel, ticagrelor and prasugrel)
  - Direct Thrombin Inhibitors
  - Other antithrombotic agents (e.g. anticoagulants)
- Renin-Angiotensin-Aldosterone System inhibitors
  - Angiotensin Converting Enzyme (ACE) inhibitors (like ramipril)
  - Angiotensin II Receptor Blockers (ARBs)
  - Direct Renin Inhibitors
- Lipid-lowering agents
  - Statins
    - Atorvastatin
    - Rosuvastatin
    - Simvastatin
    - Other statins and statin combinations
  - Non-statins (like PCSK9 inhibitors, ezetimibe, fibrates, binding resins and nicotinic acid)
- Diuretics
  - Thiazide diuretics
  - Non-thiazide diuretics
- Anti-diabetic medications
  - Insulin

- Oral hypoglycemic agents
  - Thiazolidinediones
  - Metformin and other biguanides
  - Sulfonylureas
  - Alpha glucosidase inhibitors
    - sulfonamides
    - glymidine
  - DPP-4 inhibitors
  - Glinides
  - Other oral hypoglycemic agents (incl. SGLT2 inhibitors)
- GLP-1 analogs
- Aldosterone antagonists
- Proton pump inhibitors
- Treatments for macular degeneration

Additionally, the time course of the total daily dose level of concomitant statins will be reported at baseline and tracked over time. For each patient, the daily dose will be determined as follows:

1. For each patient, the daily dose will be determined by the statin use with start/stop date.
2. The daily dose by visit will be presented for the time course of the total daily dose level.
3. For each patient, the daily dose at each visit will be defined as the median of the daily doses since the last visit.
4. The median of individual patient's dose at each visit will be used as the point estimate for the plot/summary
5. In order to have consistent timings for the visit, the visits will be calculated based on protocol visit scheduling.

For this purpose doses of different statins will be equated according to Table 5-1. Median statin dose level, and patients on each standardized dose level will be summarized over time and displayed graphically, where possible. Patients will be classified according to whether they receive no, low dose, medium dose or high dose statins at baseline and during the study. This will be done separately by time since index MI (including finer categorizations than $<$ versus $\geq$ 6 months post index-MI) and by region. If new statins become available or substantial new information regarding their lipid lowering effects becomes available, this table may have to be updated.

Table 5-1 Conversion table for statin doses

Dose intensity of statin		Low			Medium	High		
Standardized statin dose[1] [mg] (atorvastatin equivalent)	Scaling factor	2.5	5	10	20	40	80	160[2]

Dose intensity of statin		Low			Medium	High		
Standardized statin dose[1] [mg] (atorvastatin equivalent)	Scaling factor	2.5	5	10	20	40	80	160[2]
Atorvastatin (LIPITOR)	× 1		5*	10	20	40	80	160*
Lovastatin (MEVACOR)	/ 4	10	20	40	80			
Pravastatin (PRAVACHOL)	/ 4	10	20	40	80			
Simvastatin (ZOCOR)	/ 2	5	10	20	40	80		
Fluvastatin (LESCOL)	/ 8	20	40	80				
Rosuvastatin (CRESTOR)	× 2		2.5*	5	10	20	40	80*
Pitavastatin / itavastatin (LIVALO)	× 20				1	2	4	
Ezetimibe 10 mg + Simvastatin (VYTORIN, INEGY)	× 2 standardized statin dose				10/10	10/20	10/40	10/80
Any other statin + ezetimibe or resin binders (e.g. colesevelam, cholestyramine, colestipol)	× 4 standardized statin dose							

* off label dosing

[1] All other other drugs containing a statin should be reported for the statin dose only (including the following):
Statin + fenofibrate, + clopidogrel, + acetylsalicylic acid, + amlodipine, + ramipril

[2] Efficacy response curves flatten at the maximal equivalence of atorvastatin 160 mg or rosuvastatin 40 mg: further LDL lowering attempts with other lipid lowering drugs do not yield further LDL lowering. I.e. any calculated standardized statin dose > 160 mg will be considered as a standardized statin dose of 160 mg.

6 Efficacy evaluation

The primary analysis and all analyses of secondary/exploratory variables will be conducted according to the intention-to-treat principle on the Full Analysis Set (FAS). Unless otherwise specified all time-to-event analyses will be based on events occurring during the double-blind phase. Unless otherwise specified "treatment groups" will refer to the four treatment groups canakinumab 300 mg, 150 mg, 50 mg or placebo. Comparing these separate active doses individually versus placebo will be the main method of analysis, but analyses of all canakinumab doses pooled versus placebo, as well as the active doses versus each other will also be conducted and dose response will be considered as described in section 6.5.

6.1 Variables

An overview of the primary, key secondary and other secondary variables as well as their components is given in Table 6.1. At the end of the study all endpoints will have been adjudicated by the Clinical Events Committee (CEC). The investigator reported events will only be considered as supportive. In order to assess the robustness of results at interim analyses the DMC will also be informed about events that have either been confirmed by adjudication, or reported by the investigator and not yet adjudicated. Events that have either been confirmed by the CEC or reported by the investigator but not yet been adjudicated will primarily be used for DMC activities to account for the time lag in adjudication.

Table 6-1 Primary, key secondary and secondary variables for CANTOS

Endpoint (variable is time	Adjudication	Investigator	CEC confirmed or non-

to endpoint)	committee (CEC) confirmed	reported	adjudicated investigator reported ("unrefuted")
Major adverse cardiovascular events (MACE)	Primary	Supportive	Primarily for DMC monitoring
CV death	Supportive	Supportive	Primarily for DMC monitoring
fatal or non-fatal Myocardial infarction	Supportive	Supportive	Primarily for DMC monitoring
fatal or non-fatal stroke	Supportive	Supportive	Primarily for DMC monitoring
MACE or hospitalization for unstable angina requiring revascularization	Key secondary	Supportive	Primarily for DMC monitoring
hospitalization for unstable angina requiring revascularization	Supportive	Supportive	Primarily for DMC monitoring
New onset of diabetes	Key secondary	Primarily for DMC monitoring	Primarily for DMC monitoring
All-cause mortality	Secondary	Primarily for DMC monitoring	Primarily for DMC monitoring
All-cause mortality or myocardial infarction or stroke	Secondary	Supportive	Primarily for DMC monitoring

6.1.1 Endpoint adjudication process

An external independent blinded adjudication committee will adjudicate all deaths, strokes, transient ischemic attacks, MIs, hospitalization for unstable angina requiring revascularization, new onsets of diabetes, all hospitalizations with adjudicatable information, and any other events that may be deemed appropriate for adjudication as the trial progresses.

As shown in Figure 6-1 there are 3 ways in which cases will be identified and forwarded to the adjudication committee.

The first identification process is by the investigator filling out an endpoint eCRF page. These pages trigger a notification to the Endpoint Coordinating Center (Aptiv) that a potential endpoint has occurred. Aptiv then assembles an adjudication package for the clinical endpoint adjudication committee (CEC).

The second identification process is by the sponsor clinical team reviews of the adverse events reporting via the clinical trial database, and ARGUS SAE reporting system.

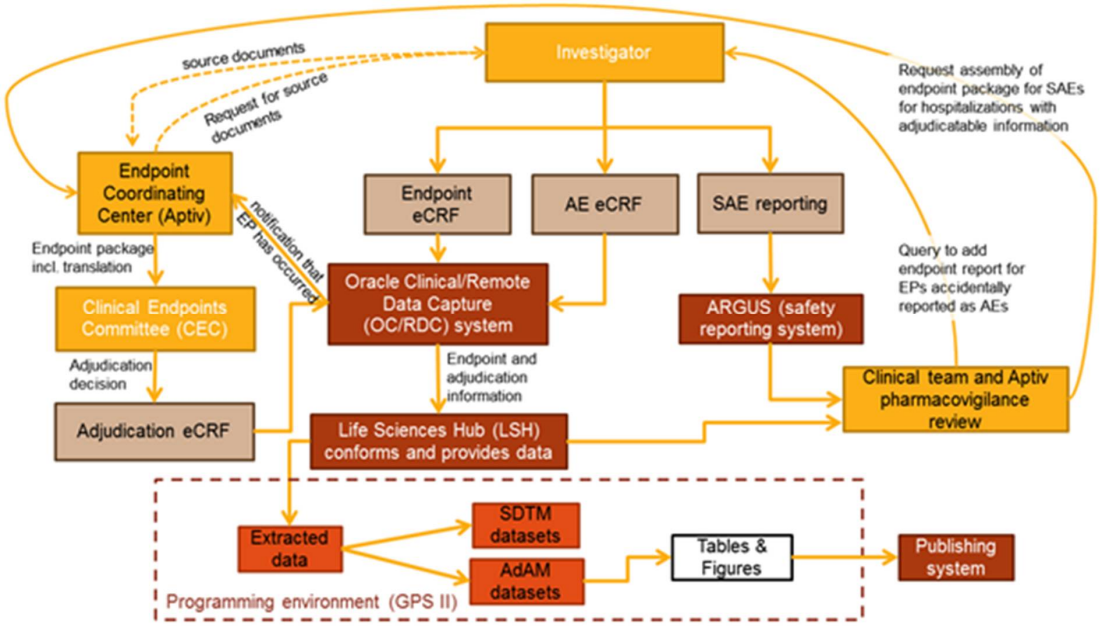
The third identification process is by Aptiv (a "third party") pharmacovigilence reviews of the Novartis ARGUS SAE reporting system of the SAEs which the sponsor clinical team did not send for adjudication.

This is done to ensure all hospitalizations with adjudicatable data are sent for potential MI or stroke adjudication. Adjudication packages for all SAEs requiring hospitalizations with adjudicatable material identified by these reviews that had not been previously been identified

by the investigator as a Study Endpoint, are also sent to the Endpoint Coordinating Center by Aptiv.

Once the Endpoint Coordinating Center (Aptiv) receives an endpoint notification, an adjudication packet consisting of source documents from the site is created and sent to the adjudication committee. The adjudication committee reviews the source documents, determines if the endpoint did or did not occur, and then fills out the adjudication eCRF page.

Figure 6-1 Simplified overview of the adjudication process



6.1.2 Primary efficacy variable

The primary efficacy variable is the time to first occurrence of a major adverse cardiovascular event (MACE) confirmed by Clinical Events Committee (CEC) adjudication, which is a composite endpoint consisting of CEC confirmed cardiovascular death, CEC confirmed MI, and CEC confirmed stroke.

The primary clinical endpoint MACE is a well-established endpoint for CV trials. An external Clinical Events Committee (CEC) will review and adjudicate all clinical events that constitute MACE and the key components of secondary endpoints on a blinded basis as described in section 6.1.1.

The individual components of MACE will be also analyzed as part of the primary efficacy analysis.

- Cardiovascular death
- Myocardial infarction (fatal or non-fatal)
- Stroke (fatal or non-fatal)

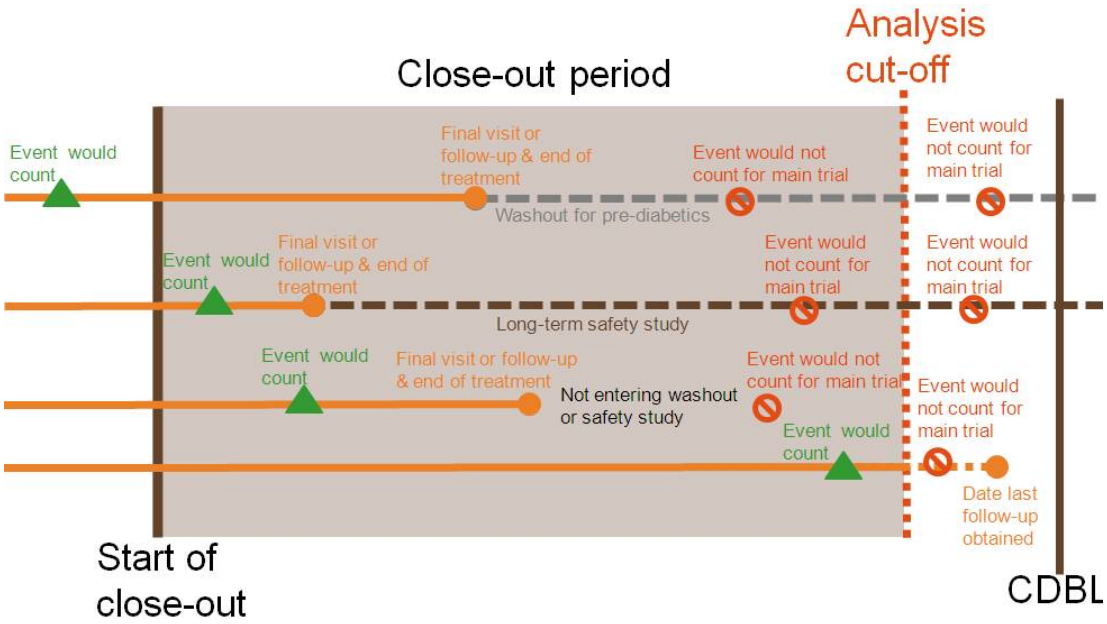
The time-to-event is computed as the number of days from randomization to the onset of the primary endpoint event. In the case of patients dying due to a MI, the date of the MI and not the date of death is considered to be the date of the endpoint. Data on patients who do not reach the primary endpoint by the study end date will be censored at the latest date they are known to be at risk.

Unless otherwise specified all time-to-event analyses will be based on events occurring during the double-blind phase (i.e. both the double-blind treatment phase and the post-treatment phase). This means that only events between a patient's randomization and the first of either

1. the patient's entry into the wash-out period (= end of study visit for the main study),
2. or the patient's entry into the long-term safety extension study (=end of study visit for the main study),
3. or for those patients proceeding to neither wash-out period nor safety extension the patient's end of study visit, but only if it occurred during the close-out period,
4. or otherwise the analysis cut-off

will be counted in these analyses as shown in Figure 6-2.

Figure 6-2 Illustrative examples of events counting for the primary analysis



Note: for patients entering the washout for pre-diabetics or the long-term safety study, events would be appropriately reported as part of the respective reports. Events occurring after study completion in patients not entering either washout or long-term safety study may still be subject to SAE reporting requirements and will be reported accordingly as per Novartis processes, if applicable.

Reporting of type of first endpoint

The type of first endpoint will be identified as

- the first primary endpoint component (CV death incl. fatal MI or fatal stroke, non-fatal MI and non-fatal stroke) that occurs after randomization

- if more than one endpoint occurs on the same day, then for the purpose of reporting the type of the first endpoint a fatal event will be reported by preference (i.e. CV death in preference to a fatal-MI or fatal-stroke and these in turn in preference to a non-fatal MI or non-fatal stroke)
- should more than one endpoint fulfill the criteria above, then all of these will be reported (e.g. in case of both a non-fatal MI and non-fatal stroke on the same day "non-fatal MI and stroke" will be reported).

Note that the above only concerns the reporting of the type of the first endpoint. In the majority of tables the components of the primary endpoint will be shown separately and a patient may contribute to the numerator for no, one, two or all three components of the primary endpoint.

6.1.3 Key secondary efficacy variables

The following key secondary variables will be used in the analyses:

- Time to the first occurrence of an adjudication committee confirmed composite cardiovascular endpoint consisting of the components of the primary endpoint and hospitalization for unstable angina requiring unplanned revascularization
- Time to adjudication committee confirmed new onset of type 2 diabetes among those with pre-diabetes at randomization (i.e. excluding those that are normoglycemic at baseline)

6.1.4 Other secondary efficacy variables

The following other secondary efficacy variables will be used in analyses:

- Time to first event of MI, stroke, and all-cause mortality composite
- Time to all-cause mortality

Although all-cause mortality is considered a very important secondary endpoint due to its importance as both an efficacy and safety outcome, it is not part of the pre-specified testing procedure for primary and key secondary endpoints, as the expected number of deaths in the trial would not have ensured adequate power for this analysis.

6.2 Summarizing results across centers, countries and regions

As the target number of patients with a primary endpoint is not much larger than the number of centers, time-to-event analyses will be conducted on the pooled data from all centers without taking the center into account. However, the consistency of results by region will be explored.

6.3 Statistical hypothesis, model, and method of analysis

The primary analysis and all analyses of secondary/exploratory variables unless otherwise stated will use the Full Analysis Set (FAS), which reflects the intention-to-treat principle.

The familywise type I error rate for this trial will be controlled at the one-sided 2.5% level. One-sided testing at the 2.5% level constitutes an equivalent level of evidence as two-sided testing at the 5% level. Two sided p-values will also be provided.

6.3.1 Primary variable

The primary statistical null hypotheses are

- H_{11}: The hazard rate of first adjudication committee confirmed MACE in the canakinumab 300 mg dose group is greater than or equal to the hazard rate of the placebo group
- H_{21}: The hazard rate of first adjudication committee confirmed MACE in the canakinumab 150 mg dose group is greater than or equal to the hazard rate of the placebo group
- H31: The hazard rate of first adjudication committee confirmed MACE in the canakinumab 50 mg dose group is greater than or equal to the hazard rate of the placebo group.

Each null hypothesis is tested against the one-sided alternative that the hazard rate is smaller for the respective active dose group than for the placebo group.

These hypotheses will be tested by comparing each dose to placebo with a log-rank test stratified by time since index MI (< 6 months and ≥ 6 months) and trial part on the full analysis set (FAS) according to the intent-to-treat principle. The stratification according to trial part entails some statistical inefficiency compared to a trial that would have had 4 treatment groups from the start, especially for the 50 mg dose, because comparisons against the placebo group in trial part 1 are only indirect via the comparisons versus other doses in trial part 2. However, this approach ensures that no biases arise e.g. due to differences over time between the two trial parts in the recruited patient population or background medical care. While investigators are not blinded to the assignment of patients to randomization plan A or B, this is not believed to introduce any biases with respect to the assessment of the primary endpoint and the standard or care provided to patients, because patients have an equal chance of being on an active treatment group under either randomization plan. Thus, it was not considered necessary to also stratify the analysis in this respect, but a sensitivity analysis will be conducted. A sensitivity analysis with respect to the consistency of treatment effects in the two parts of the trial will also be performed.

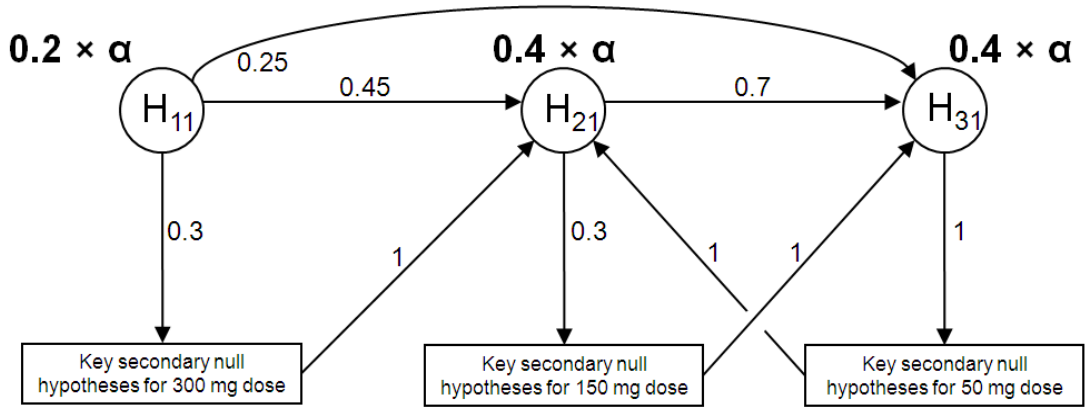
Note that no assumption of proportional hazards is necessary to test whether there is a higher probability of MACE in canakinumab than on placebo, because the employed stratified log-rank tests are valid even without proportional hazards. This assumption is only necessary to calculate estimated hazard ratios with confidence intervals for the effect of treatment (Bland and Altman 2004).

The family-wise error rate will be controlled at the two interim analyses and the final analysis using the closed testing procedure shown in Figure 6-4 based on the graphical method of Bretz et al. (Bretz, et al 2009); however, in intersection null hypotheses involving the primary null hypotheses for the 300 mg, 150 mg or 50 mg doses these primary null hypotheses will be tested using a weighted version of Dunnett's test (Dunnett 1955). Specifically this means that for any intersection hypothesis from the full closure that contains at least two of H_{11}, H_{21} and H_{31}, a weighted Dunnett test amongst the primary null hypotheses is performed with the overall significance level for that test and the weighting chosen according to the weights assigned to these null hypotheses by the update algorithm of the graphical method. The nominal adjusted significance levels based on the weighted Dunnett test are always slightly larger than the corresponding Bonferroni levels would be. For example the mvtnorm package in R (Genz and Bretz 2009) calculates the nominal Dunnett significance levels at the final

analysis for the 300 mg, 150 mg and 50 mg doses versus placebo adjusting for the interim analysis in the test of the global null hypothesis to be 0.5500504%, 1.1001008% and 1.1001008%, respectively, as compared to Bonferroni levels of 0.49%, 0.98% and 0.98%. If other non-primary null hypotheses in such an intersection hypothesis have non-zero weight on the basis of Figure 6-4, the intersection null hypothesis will be rejected if either (a) these other null hypotheses can be rejected at a Bonferroni significance level based on that weight or (b) the primary null hypotheses can be rejected based on the weighted Dunnett test.

To illustrate the link between trial objectives and the close testing procedure, it may be helpful to consider what the procedure might have looked like, if the Dunnett test had not been used. This is shown in Figure 6-3. As discussed in detail below, introducing a Dunnett test required modifications with several additional vertices to ensure consonance (see Figure 6-4).

Figure 6-3 Possible closed testing procedure if Dunnett test had not been used



All other intersection hypotheses are tested with a weighted Bonferroni test. Protection of the family–wise error rate at level alpha is still guaranteed when the transition weights on the directed edges are chosen as in Figure 6-4 (see comment below the figure) and all the tests on secondary variables are performed at the level resulting from the graphical procedure. The consonance of the test procedure (Brannath and Bretz 2010) has also been ensured as described below.

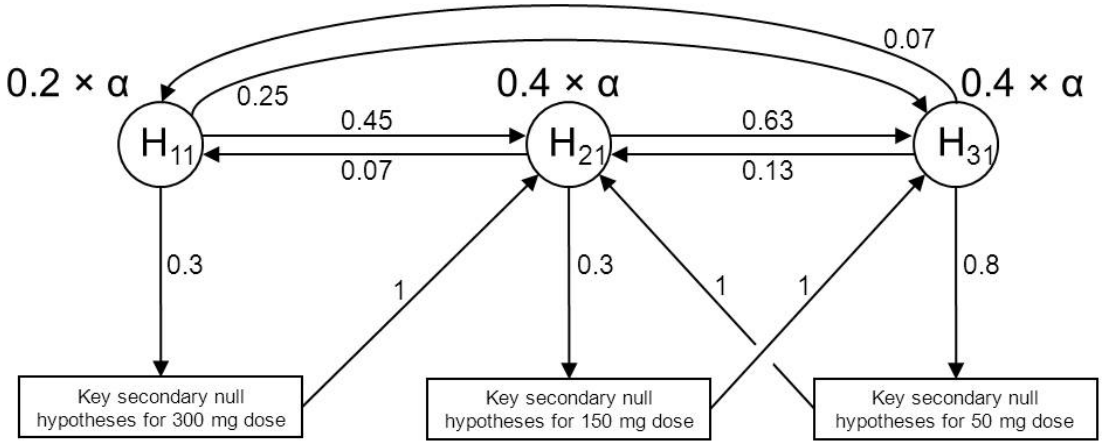
The testing procedure in Figure 6-4 initially splits the entire available significance level (at the final analysis 2.45%) between the three primary null hypotheses relating to the three doses (at the final analysis 20% of 2.45% = 0.49% for the primary null hypothesis of the 300 mg dose, 40% of 2.45% = 0.98% for that of the 150 mg dose and 40% of 2.45% = 0.98% for that of the 50 mg dose). These weights were chosen by balancing the prior expectations about the efficacy dose response relationship versus the potential for a better risk benefit ratio with lower doses. In particular, one aim was to ensure that there would be at least 80% power for the 50 mg dose to become significant assuming a 20% relative risk reduction for all doses. In the process of ensuring this, the weight for the 300 mg dose was reduced more than that of the 150 mg, because a higher dose is only of interest if it demonstrates a better efficacy than lower doses. This means that when the other doses are not effective the 300 mg dose would

only become significant with a relative risk reduction that is at least in the region of 17.5%, while for the 150 mg dose this would already be the case with relative risk reductions below 16%. However, this was considered acceptable in order to ensure the desired operating characteristics for the 150 mg and 50 mg dose.

Key secondary variables for a dose are tested using a weighted Bonferroni-Holm procedure (Holm 1979) only after successful rejection of the primary null hypothesis for that dose. In that case, a higher fraction of the local significance level that is passed from the primary null hypothesis for a dose to the key secondary endpoint for the same dose is assigned to the secondary CV composite endpoint (90%) than to the new onset of diabetes endpoint (10%). The details for the key secondary endpoints are more fully illustrated in Figure 6-5 in section 6.3.2, which discusses the key secondary efficacy variables.

Note that if the primary endpoint for the 300 mg dose (null hypothesis H_{11}) is rejected 45% of the local significance level assigned to that null hypothesis is shifted to the primary endpoint for the 150 mg dose (null hypothesis H_{21}) and 25% to the primary endpoint for the 50 mg dose (null hypothesis H_{31}). This reflects the possibility that lower doses could potentially have a better safety profile than higher doses; hence, it would be desirable to demonstrate the efficacy of lower doses even after demonstrating the efficacy of a higher dose. In contrast, the main reason why some of the local significance level assigned to lower doses is shifted to higher doses is to preserve the consonance of the test procedure; i.e. to avoid a situation in which e.g. the primary null hypothesis for the 300 mg would be rejected by the weighted Dunnett test, but could not be rejected by the chosen closed testing procedure due to insufficient alpha being assigned to some intersection null hypotheses.

Figure 6-4 Closed testing procedure for primary and key secondary endpoints



When the primary null hypothesis for a dose is rejected, some of the local significance level assigned to that primary null hypothesis is passed to the key secondary null hypotheses for the same dose. These are then tested using a weighted Bonferroni-Holm procedure at the available local significance level with weights of 90% for the key secondary CV composite and 10% for the key secondary new onset of diabetes endpoint. Only if both key secondary null hypotheses for a dose are rejected, will any of the local significance level assigned to these null hypotheses be passed on to null hypotheses for other doses. See Figure 6-5 for a version of the graph showing full details of the Bonferroni-Holm procedure for the key secondary endpoints.

Two efficacy interim analyses, at which the trial could be stopped for demonstrated efficacy, or one or more active arms could be stopped for futility, will be performed respectively after

50% and 75% of the target number of 1,400 patients have experienced a primary endpoint. Futility criteria and the criteria other than purely formal statistical significance required for stopping the trial for demonstrated efficacy will be specified in the Data Monitoring Committee charter. Protocol amendment 8 introduced an additional early futility analysis to be performed at approximately 30% of the target number of 1400 patients have experienced CEC confirmed MACE. The analysis plan of the early futility was discussed in a separate document.

A fixed Bonferroni split of the one sided significance level will be used to account for the two efficacy interim analyses and the final analysis, with a significance level of 0.01% for the first and 0.04% for the second efficacy interim analysis. I.e. the closed testing procedure will be performed with an one-sided significance level of 0.01% at the first efficacy interim analysis, with an one-sided significance level of 0.04% at the second efficacy interim analysis and with an one-sided significance level of 2.45% at the final analysis. In this fashion the familywise type I error rate will be controlled at the overall (one-sided) significance level $\alpha = 2.5\%$.

No multiplicity adjustment will be made for the additional early futility analysis, because it will not result in rejecting a null hypothesis for efficacy superiority.

The appropriate nominal weighted Dunnett significance levels will be calculated e.g. using the mvtnorm R package (Genz and Bretz 2009). For the example of the global null hypothesis this can be done using R code (or corresponding SAS code) similar to the following

```
library(mvtnorm)
alpha <- 0.0245 # level at which Dunnett test is performed
rho <- 0.5 # assumed correlation of test statistics
corr <- (1-rho)*diag(3)+rho # correlation matrix
weight <- c(0.2,0.4,0.4) # weights for hypotheses in Dunnett test
alphaw <- alpha*weight
MVN <- function(alpha1, w, corr, alpha){
      x<-qnorm(1-alpha1*w)
      return(1-pmvnorm(upper=x,corr=corr) - alpha)
      }
opt3 <- uniroot(MVN, lower = alpha, upper = 2*alpha, w=weight,
corr=corr, alpha=alpha, tol=1E-12)
critwDun <- qnorm(1-opt3$root*weight)
nominal <- opt3$root*weight
```

The hazard ratios and their associated confidence intervals will be estimated by means of a (Cox 1972) proportional-hazards model stratified by time since index MI (< 6 months, ≥ 6 months) and by trial part (trial part 1, trial part 2) using treatment (canakinumab doses and placebo) as a factor in the model. This will be done using SAS code similar to the following (or equivalent code in another programming language such as R):

```
proc phreg data=dataset;
  class treatment(ref="Placebo") <time since index MI> <trial part>;
```

```
    model time*event(0) = treatment / ties=exact risklimits;
    strata <time since MI > <trial part>;
run;
```

Should one of the three active arms be stopped due to safety reasons or futility, then thereafter the pre-specified testing procedure will be performed for the other arms treating all null hypotheses for the stopped arm as non-rejected. For patients whose treatment is stopped as a result of a data monitoring committee recommendation to suspend treatment in one dose group, follow-up for cardiovascular (CV) and safety events will continue. Since these patients will not receive further study medication, less frequent follow-up may be conducted every 6 months. Continued follow-up would likely enhance understanding of the safety of the other remaining dose groups as well. Follow-up will simply continue in all scenarios until 1,400 patients have had a primary endpoint and the only difference to the pre-planned study conduct will be that the patients in the stopped treatment arms are not being treated after the DMC decision point.

Supportive, sensitivity and subgroup analyses for the primary endpoint

The components of the composite primary efficacy endpoint (CV death, fatal or non-fatal MI, fatal or non-fatal stroke) will also be analyzed individually in order to evaluate their contributions to the overall treatment effect. No adjustment for multiplicity is foreseen for this purpose.

The three pooled canakinumab doses will be compared to placebo on the primary composite endpoint and its components, because in case of similar efficacy on all three doses this would be the most powerful test of the scientific hypothesis addressed by this trial. Additionally, when all three doses have similar efficacy, such a pooled analysis approach may provide the most precise information on the effects in subgroups.

Dose response will be evaluated using the methods discussed in section 6.5. Additionally, comparisons between the canakinumab doses based on the primary model will also be reported.

Kaplan-Meier type analyses will be presented as described in section 6.4 overall and by trial part to summarize the time to first event in the composite endpoint, by presenting the time-dependent cumulative frequency and percentage of patients who reach the primary composite endpoint by treatment group.

Additionally, log time by treatment interaction will be evaluated to identify violations in the proportional hazards assumption, which might indicate a time-varying treatment effect. An Anderson-Darling type test based on a score process (cumulative sum of the Schoenfeld residuals) as recommended by Kvaløy and Neef (Kvaløy and Neef 2004) will be performed. For each trial arm within each trial part –log(S(time)) vs. time and log(–log(S(time))) vs. log(time) will be plotted.

To ensure that any unblinding of patients during the double-blind phase had no meaningful impact on the overall study results, a sensitivity analysis of the primary endpoint will be performed by excluding data from all patients who were unblinded during the double blind phase of the study (i.e. all the unblinded patients will be censored at the time of unblinding).

The primary variable and its components will also be analyzed on the PPS1. Additionally, in an on-treatment analysis on the FAS, patients will be considered censored at the latest 28 days after the end of the double-blind treatment phase, which corresponds to up to 119 days after the last study drug injection based on the long elimination half-life of the drug. 91 days constitute a bit over 3 half-lives and 28 days add an additional half-life. In the on-treatment analysis patients will stay in the risk set until this point unless their censoring date occurred earlier and will not leave and re-enter the risk set due to treatment interruptions. Besides adjudicated endpoints investigator reported outcomes will also be analyzed on the FAS.

Once the results become available a covariate adjusted analysis may be considered. This covariate-adjusted Cox-regression model will consider the following pre-specified baseline covariates: linear age, sex, race, linear BMI, smoking status, region as defined in section 2.2, linear baseline log hsCRP, type of qualifying MI (STEMI/NSTEMI/Unknown), glycemic status, duration of diabetes for diabetic patients, hypertension, linear baseline systolic blood pressure, linear and quadratic baseline diastolic blood pressure, history of heart failure, dyslipidemia, linear baseline LDL-C, linear baseline HDL-C, linear baseline triglycerides, linear number of prior MIs, prior PCI, prior TIA/stroke, linear eGFR, no/low or medium dose/high dose statin use at baseline as defined in section 5, baseline aspirin therapy, baseline P2Y12 therapy, RAAS inhibitor use, beta blocker use, to account for other factors that might affect prognosis.

Furthermore, the pre-specified subgroup analyses will be conducted for the subgroups listed in section 2.2. Results will be presented graphically as forest plots. The objective of the subgroup analyses is to evaluate the consistency of treatment effects across a wide variety of patient groups. For this purpose the availability of data from three different doses should be helpful, because most subgroup effects would be affect all doses to some extent, which provides an additional way of identifying spurious findings that occurred by chance. Additional subgroup analyses will be considered and potentially pre-specified prior to unblinding of trial database for final analysis. It is clear that due to the number of subgroups a substantial number of totally spurious numerical imbalances in treatment effects between subgroups has to be expected – including some with an interaction p-value ≤ 0.05 and/or with apparently no or reversed effects. The association between changes in hsCRP and outcomes will also be explored.

To assess whether pooling randomization plan A and B in trial part 2 is appropriate, the placebo groups in randomization plans A and B will be compared against each other, the 150 mg groups in randomization plan A and B will be compared and the 150 mg versus placebo contrasts will be compared qualitatively between randomization plan A and B.

As a further sensitivity analysis in this respect, randomization plan will be used as an additional stratification factor in the primary model. This analysis will use SAS code similar to the following (where randomization plan would be a 3 level stratification factor with 1 level for trial part 1 and two further levels for each randomization plan in trial part 2) or equivalent code in another programming language such as R:

```
proc phreg data=dataset;
  class treatment(ref="Placebo") <time since index MI>
      <randomization plan>;
```

```
    model time*event(0) = treatment treatment*<randomization plan>
        / ties=exact risklimits;
    strata <time since index MI> <randomization plan>;
    hazardratio treatment / diff=ref cl=both;
run;
```

A sensitivity analysis with respect to the consistency of treatment effects in the two parts of the trial will also be performed. This analysis will use SAS code similar to the following or equivalent code in another programming language such as R:

```
proc phreg data=dataset;
  class treatment(ref="Placebo") <time since index MI> <trial part>;
  model time*event(0) = treatment treatment*<trial part>
      / ties=exact risklimits;
  strata <time since index MI> <trial part>;
  hazardratio treatment / diff=ref cl=both;
run;
```

Calculation of multiplicity adjusted one- and two-sided p-values

Multiplicity adjusted p-values will be calculated for each null hypothesis as the smallest significance level at which one can reject that null hypothesis using the testing procedure shown in Figure 6-4 while also taking into account the interim analyses. For this purpose the algorithm described by Bretz et al. (2009) will be applied to the unadjusted one-sided p-values and the resultant p-values (adjusted only for the multiple endpoints and doses) will be adjusted for the interim analyses by scaling them by a factor of 250 (=0.025/0.0001) at the first efficacy interim analysis, 62.5 (=0.025/0.0004) at the second efficacy interim analysis and 0.025/0.0245 (≈1.02) at the final analysis. Because a weighted Dunnett test will be used for any intersection hypothesis from the full closure that contains at least two of H_{11}, H_{21} or H_{31}, the algorithm of Bretz et al. (2009) needs to be extended. For this purpose the weights w_{11}, w_{21} and w_{31} used as part of that algorithm would be defined as the respective Dunnett level divided by the overall significance level at the respective analysis.

For example, for the global null hypothesis instead of w_{11}=0.2, w_{21}=0.4 and w_{31}=0.4 as for a Bonferroni test based procedure – for which $w_{11} + w_{21} + w_{31} \leq 1$ would always hold – instead $w_{11} + w_{21} + w_{31} > 1$ would hold in this case. For example, using the nominal Dunnett significance levels for 300 mg, 150 mg and 50 mg doses at the final analysis calculated using the mvtnorm package in R as described earlier in section 6.3.1, one obtains w_{11} = 0.5500504% / 2.45% ≈ 0.2245103, w_{21} = 1.1001008% / 2.45% ≈ 0.4490207 and w_{31} = 1.1001008% / 2.45% ≈ 0.4490207.

In case health authorities, journals or the data monitoring committee require two-sided p-values, these will be provided in a manner that firstly ensures that the test decision on the rejection of the primary and key secondary null hypotheses remains unchanged and that secondly uses in principle the same testing procedure for evaluating the potential superiority of placebo over each dose of the test drug.

On this basis, the same test procedure as shown in Figure 6-3 will also be conducted in a one-sided fashion on the 2.5% significance level to test for the superiority of placebo over each canakinumab dose arm. The multiplicity adjusted two-sided p-values for each canakinumab dose arm will then be calculated as the minimum out of

- 2 × the multiplicity adjusted one-sided p-value for the superiority of that canakinumab dose arm over placebo,
- 2 × the corresponding multiplicity adjusted one-sided p-value for the superiority of placebo over that canakinumab dose arm versus
- and 1.

Exploration of dose response relationship and the effects of induction dosing in terms of cardiovascular endpoints

The method described in section 6.5 will be applied to assess dose response on cardiovascular endpoints over the whole duration of the trial.

It will be explored whether the early high induction dose regimen in 300 mg canakinumab arm has an impact on early (within 90 days of randomization) primary and secondary clinical cardiovascular events when compared to the placebo arm and to the 150 mg and 50 mg canakinumab arms, which have no early high induction dose regimen. For this purpose the primary endpoint and its components will be assessed over 90 days post-randomization. Similarly, the primary endpoint and its components will also be assessed at 6 months and 1 year, repeatedly.

6.3.2 Key secondary efficacy variables

The following hypotheses will be tested with respect to the key secondary variables for the canakinumab 300 mg dose versus placebo

- H_{12}: The hazard rate of first adjudication committee confirmed secondary composite CV endpoint in the canakinumab 300 mg dose group is greater than or equal to the hazard rate of the placebo group
- H_{13}: The hazard rate of adjudication committee confirmed new onset of diabetes for pre-diabetic patients in the canakinumab 300 mg dose group is greater than or equal to the hazard rate of the placebo group

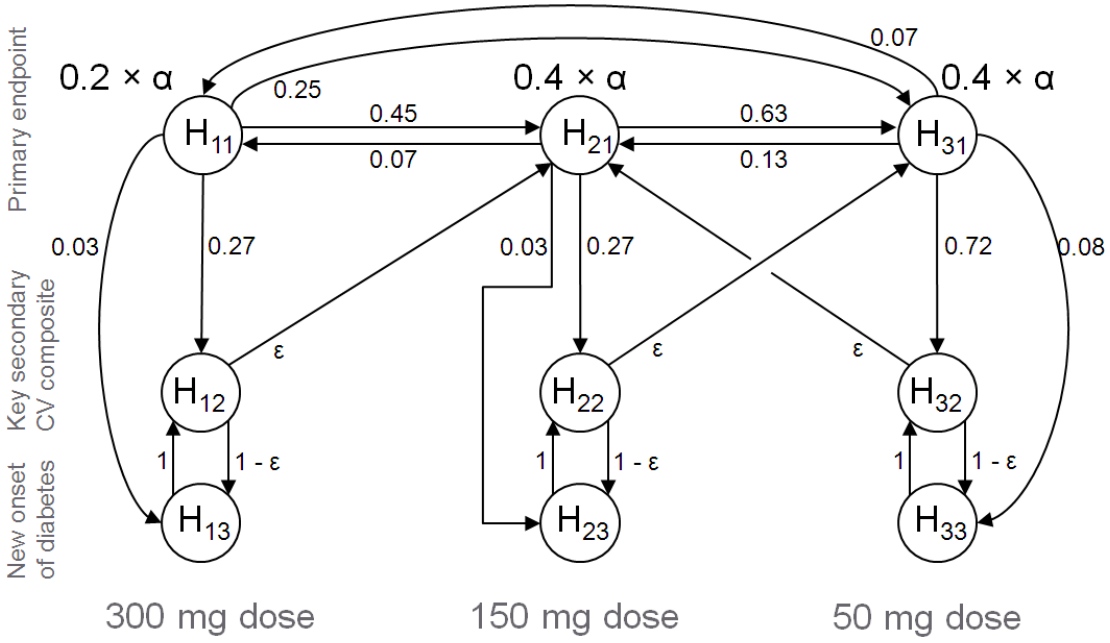
Each null hypothesis is tested against the one-sided alternative that the hazard rate is smaller for the canakinumab 300 mg dose group than in the placebo group. The corresponding hypotheses for the comparison of the canakinumab 150 mg dose versus placebo are H_{22} for the secondary composite CV endpoint and H_{23} for the new onset of diabetes endpoint. For the 50 mg dose they are H_{32} for the secondary composite CV endpoint and H_{33} for the new onset of diabetes endpoint.

All key secondary efficacy variables will be analyzed on the FAS and PPS1with a log-rank test stratified by time since index MI and trial part. The hazard ratios will be estimated using a Cox regression model stratified by time since index MI and trial part.

Kaplan-Meier plots showing each treatment will be provided overall and by trial part as described in section 6.4. The multiplicity adjustment used to protect the familywise type I

error rate is shown in Figure 6-4 and showing the full details of testing the key secondary endpoints in Figure 6-5. For each dose analyses of key secondary endpoints will be conducted even if the primary null hypothesis for the dose has not been rejected, but formally no rejection of the null hypotheses for the key secondary endpoints will be possible in that case.

Figure 6-5 Closed testing procedure with full details of testing of key secondary endpoints



This figure as compared to Figure 6-4 shows the full details of the Bonferroni-Holm procedure for the key secondary endpoints in a graphical form, but is otherwise identical in content.

Based on this testing procedure, once the primary null hypothesis for a dose has been rejected the key secondary endpoints for that dose are tested using a weighted Bonferroni-Holm test (Holm 1979) at the available local significance level for the key secondary endpoints for that dose. The weighting of this Bonferroni-Holm procedure will be 90% for the key secondary CV composite and 10% for the key secondary new onset of diabetes endpoint.

The secondary efficacy variable corresponding to new onset diabetes in patients with pre-diabetes at randomization will be the time from randomization to the first of repeated FPG $\geq$ 126 mg/dL or the first of repeated HbA1c $\geq$ 6.5% or start of new anti-diabetic concomitant medication(s) for glucose lowering purpose. All identified cases of new onset of diabetes will be confirmed by the adjudication committee.

Due to the discrete nature of the visits when new onset of type 2 diabetes can be determined, events identified at the same visit time point as defined in section 2.3.6 for different patients will be considered as tied events and the exact method for handling ties will be used. This assumes that for each of these patients new onset of diabetes occurred at some time point since the previous visit, but that due to the impossibility of continuous monitoring of the patients the true order in which each of them progressed to diabetes is unknown (Allison 1995,

pp. 127 to 137). For this variable patients without new onset of diabetes will be considered censored at the time of their last laboratory assessment. Patients not diagnosed at a regular visit or at the study completion visit will be assigned to one of the scheduled visits as per the algorithm in section 2.3.6.

Subgroup analyses as specified in Table 2-3-1 will be conducted for the key secondary new onset of diabetes endpoint. These will include subgroup analyses by race, which could potentially influence HbA1c levels.

Given some patients may have medical conditions that elevate their HbA1c levels that are unrelated to diabetes (e.g. patients with hemoglobinopathies such as sickle cell disease, while several other conditions causing interference such as e.g. uremia, liver disease, alcoholism and drug (opiate) use are excluded from this protocol), a second set of new onset diabetes criteria will be defined. This second set of criteria will determine new onset diabetes for these patients based on having either (2 consecutive HbA1c >= 6.5 % and 2 consecutive FPG values >= 126 mg/dL from the same visits as HbA1c) or (HbA1c >= 6.5 % at one visit reported and FPG >= 126 mg/dL reported at same visit and FPG>=126 confirmed at the consecutive visit) or 2 consecutive FPG values >= 126 mg/dL. The identification of these patients will be done in a blinded fashion by a medical monitor using medical history data and other baseline data. All patients deemed not to have any of these medical conditions will be assessed for new onset diabetes as described in the first set of criteria (see paragraph above). New onset of diabetes data will be reported overall and separately for these patients in whom diagnoses based on HbA1c levels is not appropriate (defined as “FPG >= 126 mg/dl at 2 occasions” or “Confirmed prescription and use of Diabetes Drug” based on the New Onset Diabetes (Adjudication) CRF page) The analysis described above will also be performed using this alternative new onset diabetes definition.

Supportive and sensitivity analyses for key secondary endpoints

To support the analysis for the new onset of diabetes endpoint, the criteria defining new onset will be presented, the diagnostic values causing diagnosis summarized and sensitivity analyses conducted based on each criterion alone.

The three pooled canakinumab doses will be compared to placebo on the key secondary endpoints. Additionally, comparisons between the canakinumab doses will also be reported using the pre-specified log-rank test with hazard ratios reported based on Cox regression.

Additionally, Kaplan-Meier plots will be provided separately for each of the followings:

- Time to adjudication committee confirmed new onset of type 2 diabetes among those with normoglycemic at randomization
- Time to adjudication committee confirmed new onset of type 2 diabetes among those with either pre-diabetes or normoglycemic at randomization
- Time to first pre-diabetes among those with normoglycemic at randomization.

The key secondary cardiovascular endpoint will also be analyzed adjusting for the same covariates used for the covariate adjusted analysis of the primary variable.

The key secondary endpoint new onset of diabetes will also be supported by analyses using data from the study’s washout period. These analyses will be defined in a separate analysis

plan for the washout period and will be reported in a separate study report or addendum to the main study report.

6.3.3 Other secondary efficacy variables

As stated in section 6.1.3 all-cause mortality is considered a very important secondary endpoint due to its importance as both an efficacy and safety outcome, but it is not part of the pre-specified testing procedure for primary and key secondary endpoints, because given the expected number of deaths in the trial it would not have been possible to adequately power the key secondary mortality endpoint.

All-cause death and the composite of all-cause death, stroke or MI will be analyzed on the FAS and PPS1with a log-rank test stratified by time since index MI and trial part. The hazard ratios will be estimated using a Cox regression model stratified by time since index MI and trial part.

Kaplan-Meier plots showing each treatment will be provided both overall and by trial part. Patients who did not die will be considered censored at the last time they were reported to be alive.

These secondary endpoints will also be analyzed adjusting for the same covariates used for the covariate adjusted analysis of the primary variable.

The three pooled canakinumab doses will be compared to placebo on the other secondary endpoints. Additionally, comparisons between the canakinumab doses will also be reported.

6.3.4 Exploratory Efficacy variables

Exploratory time-to-event outcomes will be analyzed using Cox models including treatment with time since index MI and trial part as stratification variables, along with Kaplan-Meier analyses overall and by trial part. Exploratory continuous outcome variables (i.e. change from baseline of HbA1c, biomarkers, etc.) will be analyzed using both a repeated measures random effects analysis adjusted for baseline value, trial part, and time since index MI as a factor, as well as a descriptive analysis. For exploratory endpoints the three pooled canakinumab doses will also be compared to placebo.

Other cardiovascular disorders with a known inflammatory component

The following variables will be analyzed, as appropriate, based on the number of events observed:

- Time to other cardiovascular disorders with a known inflammatory component:
  - Time to first deep vein thrombosis/pulmonary embolism
  - Time to first supraventricular tachycardia/atrial fibrillation
  - Time to first stent thrombosis (probable or definite)
  - Time to first hospitalization or prolongation of hospitalization for heart failure or cardiovascular death due to heart failure/cardiogenic shock, and the components of this composite:
    - Time to first hospitalization or prolongation of hospitalization for heart failure

    - Time to first cardiovascular death due to heart failure/cardiogenic shock
  - Time to first event of major coronary events composite: CHD death or MI, where CHD death is defined as a death due to myocardial infarction, congestive heart failure/cardiogenic shock, directly related to revascularization, due to arrhythmias, due to witnessed sudden death, unwitnessed sudden death seen within 24 hours, unwitnessed death, death due to unknown cause or due to other vascular causes identified as Ischemic Heart Disease (i.e. fulfilling the narrow "Ischaemic heart disease" SMQ)
- Time to first event of total vascular events composite consisting of primary endpoint, hospitalization for unstable angina, or for any other non-coronary ischemic event (transient ischemic attack or limb ischemia), any revascularization procedure (coronary and non-coronary), coronary angiography, and limb amputation
- Time to first event of coronary revascularization procedures (PCI or CABG)
- Time to first event of stroke by etiology

As long as sufficient events (e.g. >20 events per covariate) are available, the same covariates as for the primary endpoint will be used in covariate adjusted analyses.

In addition, the model may also include the covariates listed below if appropriate:

- For stent thrombosis, history of previous stents (and type of stent) will be taken into account, as this substantially influences the risk of stent thrombosis; without a previous stent an event requiring stenting would first have to occur, before a stent thrombosis could occur. For deep vein thrombosis/pulmonary embolism, a limited list of covariates will be used: linear age, sex, race, linear BMI, linear height, use of warfarin or other anticoagulants at baseline, history of deep vein thrombosis or pulmonary embolism.
- For the supraventricular tachycardia/atrial fibrillation endpoint, a limited list of covariates will be used: history of supraventricular tachycardia, history of atrial fibrillation, and use of medications such as digoxin at baseline, as well as age group (< 65, ≥ 65), sex and race.

Nephropathy and renal function

Time to nephropathy as assessed by urine albumin/creatinine ratio (≥ 30 mg/mmol) in patients with T2DM or pre-diabetes at baseline will be analyzed.

Only patients with a baseline urine albumin/creatinine ratio that is < 30 mg/mmol or missing will be included in this analysis. If nephropathy occurs, the time of the event will be the visit at which the laboratory sample was drawn. The analysis will be conducted in the same fashion as for new onset of diabetes with the same rules for censoring and tied event times.

Subgroup analyses based on the basis for diabetes diagnosis (FPG or HbA1c based versus only based on diabetes medication use) will be provided.

Additionally, the occurrence of nephropathy based on adverse event reporting, occurrence of the narrow SMQ Acute Renal Failure, doubling of serum creatinine, non-cardiovascular death due to renal failure and endstage renal disease (ESRD) defined as dialysis, renal transplant, or serum creatinine >530 μmol/L (6.0 mg/dL) will also be analyzed. An overall composite will also be provided. The laboratory data based outcomes will be analyzed in the same fashion as

the new onset of diabetes endpoint based on the visit at which the lab sample was drawn, while other outcomes will be analyzed in the same way as the primary CV endpoint. As the laboratory based events are likely to be more frequent than the other components of the composite, the composite will be analyzed as if it were laboratory data based. The continuous log-transformed urine albumin creatinine ratio will be also analyzed as well as eGFR over time and abnormalities will be considered (see also section 7.4.8).

Predictive covariates will be taken into account in all models including baseline eGFR, baseline creatinine, baseline log urine albumin creatinine ratio, age, sex, race, baseline blood pressure, history of heart failure, antihypertensive drug use and baseline glycemic status.
Glycemic control among those with type 2 diabetes

The following two variables will be analyzed to compare glycemic control between the three canakinumab doses and placebo among those with type 2 diabetes at baseline. The following variables will be analyzed

- Time to failure of glycemic control defined as HbA1c ≥ 7.5% confirmed by a second HbA1c within 6 weeks in those patients that were diabetic at baseline with a baseline HbA1c < 7.0%
- Change from baseline in HbA1c overall, to the end of study and by visit in all patients that were diabetic at baseline; by visit analyses will use mixed model repeated measures analysis as described in section 7.2..

For the time to failure of glycemic control endpoint, the analysis will be conducted in the same fashion as for new onset of diabetes with the same rules for censoring and tied event times.

Both HbA1c analyses will use baseline value, and baseline BMI as continuous linear covariates, duration of diabetes and the use of diabetic medications at baseline (yes/no) as a factor in the analysis models. The effect of region will be explored in additional models.

Subgroup analyses based on the basis of diabetes diagnosis (FPG or HbA1c based versus only based on diabetes medication use) will be provided for the time to failure of glycemic control and change from baseline in HbA1c analyses.

Long-term glycemic control will also be looked at in terms of the change of slope in FPG/HbA1c increases over time using a mixed model approach.

Additionally the following will be analyzed:

- Change from baseline to each visit and to the end of study in FPG analyzed as for HbA1c
- Responder rates with respect to HbA1c ≤ 6.0%, 6.5% and 7.0% at the end of study (and by visit) including in the subsets of patients with HbA1c ≤ / > 8.0% at baseline
- Responder rates in terms of a reduction in HbA1c ≥ 0.5% at the end of study (and by visit)
- Responder rates in terms of FPG at end of study ≤ 6.1, 7.2, 7.8 or 10.0 mmol/L (≈ 110, 130, 140 or 180 mg/dL)

Change from baseline in FPG will be analyzed in an analogous fashion as HbA1c, except that baseline FPG is used in the model instead of HbA1c. Binary response variables will be analyzed using logistic regression models including the respective baseline value (HbA1c or

FPG as appropriate), baseline BMI, use of diabetic medications at baseline, duration of diabetes, treatment and region. Response rates will be analyzed over the whole trial duration using a generalized linear model with a logit link. The generalized estimated equation method with an unstructured correlation matrix as the working correlation structure and the same model covariates will be used.

Biomarkers of cardiovascular and diabetes risk

Change from baseline in biomarkers of cardiovascular and diabetes risk, including but not limited to inflammatory biomarkers, glycemic control markers, β-cell function markers, FPG and HbA1c, including achieved reductions from baseline in hsCRP and target hsCRP levels achieved (to be defined based on baseline characteristics once recruitment is completed)will be analyzed. When analyzed as a continuous variable hsCRP will be log-transformed and results reported as geometric means and ratios of geometric means with adjustment for baseline values.

Multiple occurrences of the primary composite MACE endpoint

The numbers and rates of individual components of MACE (allowing for multiple events per patient) will be analyzed on the FAS set and summarized by treatment group and trial part. For a single patient multiple MIs or strokes may be considered to have occurred. Fatal MIs or fatal strokes will only be counted as a separate event from the patient's death, if the death occurred more than 1 day (i.e. $\geq$ 2 days) after the MI or stroke. Rates will be compared between treatment groups based on Negative Binomial regression including terms for treatment, trial part, and log (time at risk) as offset variable. A 95% confidence interval will be provided for the ratio (active dose group vs. control) of rates for each component of the MACE composite endpoint. The SAS procedure GENMOD, will be used to conduct the analysis.

Occurrence of diabetic complications

The occurrence of diabetic complications such as retinopathy, nephropathy, neuropathy, foot ulcers or dermopathy will be compared between treatment groups based on adverse event reporting (and in the case of nephropathy also in terms of laboratory data) using descriptive statistics. The difference in the occurrence of such events or in nephropathy assessed by urine albumin/creatinine ratio could further support the benefit of patients indicated by improved glycemic control with canakinumab in diabetic patients or a lower incidence of new diabetes diagnoses with canakinumab in pre-diabetic patients. As this would rely on adverse event reporting as opposed to more systematic assessments and the timeframe of the trial may be too short to see an effect on such outcomes, it is possible that no difference will be seen in these events even if canakinumab were to prevent such events over a sufficiently long timeframe. For these reasons this assessment is considered a potentially supportive exploratory assessment.

As the number of events for some of these events is expected to be limited, the three pooled canakinumab doses will also be compared to placebo for these variables.

Macular degeneration

Whether patients had a history of or current macular degeneration at baseline will be identified via a suitable set of MedDRA terms applied to the reported medical history. These MedDRA terms will be pre-specified prior to clinical database lock.

In patients with age-related macular degeneration at baseline, occurrence of worsening and/or need for treatment will be looked at in terms of incidence and also using time-to-event methods corresponding to the primary analysis model (both as a composite and looking at these two endpoints separately) including ones taking into account predictive covariates. Worsening will be defined as a post-baseline AE report of the MedDRA terms also used at baseline. Similarly, the same criteria will be applied to reasons for the use of concomitant medications or non-drug interventions to identify treatment for macular degeneration. However, adverse event reports may be the most important source of information, because a treatment due to a worsening of disease as opposed to the continuation of ongoing treatment may not be distinguishable.

In patients without age-related macular degeneration occurrence thereof (same criteria as for worsening above) and/or need for treatment (same criteria as above) will be summarized and analyzed using time-to-event methods including ones taking into account predictive covariates. Kaplan-Meier type analyses will also be presented in both patient groups. The same censoring date as for the primary MACE endpoint will be used and time to event will be defined as time from randomization to the AE or medication start date.

The baseline categorization and type of reported post-baseline events will both be summarized by MedDRA preferred terms, type of concomitant medications and reasons for their use by MedDRA preferred term for each medication.

The following potentially prognostic covariates will be taken into account in analyses of macular degeneration linear age, sex, race, smoking status, linear baseline log hsCRP, alcohol use, linear baseline BMI, linear baseline SBP/DBP.

6.3.5 Patient reported outcomes and health economic analyses

Exploratory efficacy patient reported outcome variables including those related to tiredness, physical function, performance function and health status, will be generated from the Modified Ranking Scale, MFSI-SF, SF-36, SIS-16, EQ-5D, Heath State Classification, and Visual Analogue Scale.

Details of the MFSI-SF and SF-36 analyses, which are being assessed on a subset of patients in the US and predefined EU countries, are specified in the next sections.

The Modified Ranking Scale, MFSI-SF and SIS-16 analyses, part of the Stroke Functional Assessment Sub-study, will also be specified in the next sections.

The EQ-5D analyses, done on all patients in the FAS, are specified below.

6.3.5.1 Health-related quality of life (EQ-5D)

EQ-5D index is a standardized measure of health status developed by the EuroQoL Group in order to provide a simple, generic measure of health for clinical and economic appraisal (EuroQoL Group, 2009). EQ-5D essentially consists of 2 pages:

- the EQ-5D-3 Level (EQ-5D-3L) descriptive system that compromises the dimensions mobility, self-care, usual activities, pain/discomfort and anxiety/depression, with each having 3 levels (no problems, some problems, severe problems), and
- the EQ visual analogue scale (EQ VAS)

Scoring Descriptive System

The EQ-5D-3L descriptive system includes codes that indicate the level of the perceived problem. This section of the EQ-5D should be scored as follows.

- Level 1 (no problem) is coded as a "1"
- Level 2 (some problem) is coded as a "2"
- Level 3 (severe problem) is coded as a "3"

Missing values should be left blank and coded as ",". Ambiguous values (e.g., two boxes are checked for a single dimension) should be treated as missing values and coded as missing.

Scoring the VAS

The EQ-5D VAS should be scored as the number, between 0 and 100, where the response crosses the VAS. If the line does not cross the VAS, the response can still be scored by drawing a horizontal line from the end point of the response to the VAS. Missing values should be left blank and coded as ".". Ambiguous values (e.g., the line crosses the VAS twice) should be treated as missing values.

Planned reporting as part of Clinical Study Report

The following analysis populations will be used for the analysis of the EQ-5D. For each patient-reported outcome (EQ-5D descriptive system and EQ-5D VAS), the analysis population will consist of all patients in the full analysis set who have at least one baseline or post-baseline outcome measurement.

The EQ-5D descriptive system and EQ-5D VAS will be summarized descriptively by treatment group, at each visit, and EQ-5D VAS change from baseline to each visit will be summarized.

The change from baseline in EQ-5D VAS will be compared between treatment groups as follows.

Changes from baseline in EQ-5D VAS will be compared between each treatment and placebo using a linear model for repeated measures. In this model, treatment, visit (categorical variable), treatment-by-visit interaction, region, baseline EQ-5D VAS, trial part, and time since index MI (< 6 months, ≥ 6 months) will be the fixed effects. The interaction between treatment and visit will be retained in the model regardless of its significance to obtain estimates of treatment effects (i.e., least squares means) at the scheduled visits (3, 6, 12, 36,

and 48 months). Because this is event-driven the number of patients with measurements at months 36 through 48 may be too low, in which case the visits with few patient measurements will be excluded from the model. The correlation between measurements from the same patient will be modeled using a heterogeneous compound symmetry covariance structure. The variance-covariance matrix structure will be specified using a REPEATED statement with measurements repeated by patient. The parameters will be estimated using Restricted Maximum Likelihood. The denominator degrees of freedom will be calculated using the Kenward-Roger method (Kenward and Roger 1997).

6.3.5.2 Tiredness (MFSI-SF)

The Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF) is a 30-item patient-reported measure designed to assess the multidimensional nature of fatigue. There are 5 domains: general fatigue, physical fatigue, emotional fatigue, mental fatigue, and vigor, each measured by 6 items that use a 5-point graded response scale (0 = not at all to 4 = extremely). Respondents indicate the extent to which they have experienced each symptom within the past week. Higher values reflect greater fatigue on all items except the 6 vigor domain items. A total MFSI-SF fatigue score can also be generated.

Scoring the MFSI-SF

The five MFSI-SF domain scores are created by summing the 6 items in each domain of interest; domain scores range from 0 to 24. In the presence of missing data, domain scores can still be computed by substituting the average of the non-missing items for the missing item-level response into the sum-score formula, and then rounding the sum to the nearest integer. If more than one item-level response is missing in a domain, the domain score should not be computed. The MFSI-SF total score is created by summing the general fatigue, physical fatigue, emotional fatigue, and mental fatigue domain scores, and then subtracting out the vigor domain score. The MFSI-SF total score should not be computed if one or more domain scores are missing. The MFSI-SF total score ranges from –24 to 96. Higher MFSI-SF scores indicate worse fatigue.

Planned reporting as part of Clinical Study Report

The MFSI-SF analysis will be based on all patients in the full analysis set who have least one baseline or post-baseline MFSI-SF total score measurement. The MFSI-SF population will be used for the analysis of the MFSI-SF total score and domain scores. Note that the MFSI-SF was assessed on a subset of patients who are post-MI 30 days to less than 6 months in the US and predefined EU countries.

Descriptive statistics for the MFSI-SF total score and domain scores will be summarized by treatment group, at each visit, and change from baseline to each visit.

Changes from baseline in the MFSI-SF total score (and each MFSI-SF domain score) will be compared between each treatment and placebo at each scheduled visit using a linear model for repeated measures. In this model, treatment, visit (categorical variable), treatment-by-visit interaction, region, baseline MFSI-SF total score (and each MFSI-SF domain score), time since index MI (< 6 months, ≥ 6 months) and trial part, will be the fixed effects. The interaction between treatment and visit will be retained in the model regardless of its

significance to obtain estimates of treatment effects (i.e., least squares means) at the scheduled visits (1.5, 3, 6, 9, and 12 months). The correlation between measurements from the same patient will be modeled using a heterogeneous compound symmetry covariance structure. The variance-covariance matrix structure will be specified using a REPEATED statement with measurements repeated by patient. The parameters will be estimated using restricted maximum likelihood. The denominator degrees of freedom will be calculated using the Kenward-Roger method (Kenward and Roger 1997).

6.3.5.3 Health Status (SF-36)

The Medical Outcomes Study 36-Item Short Form (SF-36) is a reliable, valid, and widely used patient-reported generic health profile. The SF-36 includes 36 items that measure perceived health status across eight dimensions: Physical Functioning (10 items), Role Limitations due to Physical Health (4 items), Bodily Pain (2 items), Social Functioning (2 items), Mental Health (5 items), Role Limitations due to Emotional Problems (3 items), Vitality (4 items), and General Health Perceptions (5 items). In addition, there are 2 summary measures, the Physical Component Score (PCS) and the Mental Component Score (MCS). The SF-36 Physical Functioning subscale is a measure of physical functioning; the SF-36 Role Limitations due to Physical Health and Social Functioning subscales are measures of performance function; and the SF-36 Vitality subscale is a measure of tiredness.

Scoring the SF-36

SF-36 subscale scores are created by recoding and averaging the item responses within each subscale, and transforming the raw subscale score to a 0 to 100 scale. The PCS and MCS are weighted composites of the subscale scores. Missing values are allowed; subscale scores are computed as the average of the nonmissing items where the number of missing items is less than 50% of the subscale items. Each SF-36 score ranges from 0 to 100, with higher scores reflecting better health.

Planned reporting as part of Clinical Study Report

The SF-36 analysis population will consist of all patients in the full analysis set who have at least one baseline or post-baseline SF-36 score measurement for either PCS or MCS. The SF-36 population will be used for the analysis of the SF-36 PCS, MCS, and all domain scores. Note that the SF-36 was assessed on a subset of patients who are post-MI 30 days to less than 6 months in the US and predefined EU countries.

Descriptive statistics for SF-36 domain scores and component scores will be summarized by treatment group, at each and visit, and change from baseline to each visit.

Changes from baseline in each SF-36 score (including each SF-36 domain score) will be compared between each treatment and placebo at each scheduled visit using a linear model for repeated measures. In this model, treatment, visit (categorical variable), treatment-by-visit interaction, region, baseline SF-36 score (and each SF-36 domain score), time since index MI (< 6 months, ≥ 6 months) and trial part will be the fixed effects. The interaction between treatment and visit will be retained in the model regardless of its significance to obtain

estimates of treatment effects (i.e., least squares means) at the scheduled visits (1.5, 3, 6, 9, and 12 months). The correlation between measurements from the same patient will be modeled using a heterogeneous compound symmetry covariance structure. The variance-covariance matrix structure will be specified using a REPEATED statement with measurements repeated by patient. The parameters will be estimated using restricted maximum likelihood. The denominator degrees of freedom will be calculated using the Kenward-Roger method (Kenward and Roger 1997).

6.3.5.4 Physical Function (Modified Rankin Scale)

The Modified Rankin Scale (MRS) was given during the Stroke Functional Assessment Sub-study. MRS is a single-item, global rating of poststroke physical disability. The MRS has 6 grades, ranging from 0 (no symptoms at all) to 5 (severe disability; bedridden, incontinent, and requiring constant nursing care and attention); an additional grade of 6 has been included to the MRS to signify a patient's death. An MRS score of 0 indicates no disability.

The MRS analysis population will consist of all patients in the full analysis set that have been given this assessment after a stroke.

Scoring the Modified Rankin Scale

The MRS score is simply the 0 to 5 rating of physical disability, with an additional grade of 6 signifying a patient's death. Lower MRS scores nearer to 0 indicate better poststroke physical functioning.

Planned reporting as part of Clinical Study Report

Descriptive statistics for the MRS score will be summarized by treatment group and time point (30 and 90 days posttroke) for the first poststroke assessment (i.e., this analysis does not account for recurrent strokes). Because the MRS is scored on an ordinal scale, differences in median MRS scores will be compared between each canakinumab treatment group and placebo in each trial part and at each time point using the Wilcoxon rank sum test.

However, this comparison considers only the first poststroke assessment and does not take in to consideration that the treatment groups might be unbalanced as they consist of only patients who experienced one or more strokes. Alternatively, a generalized linear mixed model has the advantage of incorporating data from recurrent strokes, modeling outcomes that are not normally distributed, and adjusting for imbalances between treatment groups. At each time point (30 and 90 days poststroke) the outcome variable will be dichotomized as 0 (0 or 1) and 1 (2 through 6). The fixed effects in this model will be treatment, time point (categorical), treatment-by-time point interaction, trial part, and time since index MI (< 6 months, ≥ 6 months). Baseline characteristics that are unbalanced between the treatment groups will be also included in the model. The correlation between measurements within the same stroke (at 30 and 90 days) and between measurements from multiple strokes will be modeled using either random effects or covariance pattern structures.

6.3.5.5 Poststroke Fatigue (MFSI-SF) Assessment

The MFSI-SF will be administered to any patient in the US or predetermined EU countries who has a stroke at any time after enrollment in the trial.

The MFSI-SF analysis will be based on all patients in the full analysis set that have been given this assessment after a stroke.

Descriptive statistics for the MFSI-SF total score will be summarized by treatment group and time point (30 and 90 days posttroke) for the first poststroke assessment (i.e., this analysis does not account for recurrent strokes).

Differences in the MFSI-SF total score will be compared across treatment groups at each time-point using a generalized linear mixed model. A generalized linear mixed model has the advantage of incorporating data from recurrent strokes, modelling outcomes that are not normally distributed, and adjusting for imbalances between treatment groups. If the conditional distribution of the MFSI-SF total score is normal, then the identity link will be used, which is equivalent to fitting a linear mixed model; however if this distribution is not normal, another link will be used (e.g., log-normal).

The outcome will be the MFSI-SF at each time point (30 and 90 days poststroke). The fixed effects in this model will be treatment, time point (categorical), treatment-by-time point interaction, trial part, and time since index MI (< 6 months, ≥ 6 months). Baseline characteristics that are unbalanced between the treatment groups also will be included in the model. The correlation between measurements within the same stroke (at 30 and 90 days) and between measurements from multiple strokes will be modeled using either random effects or covariance pattern structures.

6.3.5.6 Physical Function and Performance Function (SIS-16)

The Stroke Impact Scale 16 (SIS-16) is a patient-reported, condition-specific measure designed to assess poststroke physical function and performance function. The instrument was developed from the 59-item Stroke Impact Scale 2.0 and includes 16 items addressing issues of Mobility (8 items), Activities of Daily Living/Instrumental Activities of Daily Living (7 items), and a single Hand Function item. For each item, respondents are asked to grade the level of difficulty experienced performing a variety of functions and tasks during the past two weeks on a 5-point graded response scale (1 = could not do at all to 5 = not difficult at all).

The SIS-16 analysis will be based on all patients in the full analysis set that have completed this assessment after a stroke.

Scoring the SIS-16

SIS-16 scores are computed by averaging the item responses and transforming the mean to a 0 to 100 scale. Where the number of missing items is less than 50% of the items, SIS-16 scores can still be computed by averaging the nonmissing items, and then transforming the mean to a 0 to 100 scale. If 50% or more item-level responses are missing, the SIS-16 score should not be computed. Higher values reflect better physical function.

Planned reporting as part of Clinical Study Report

Descriptive statistics for the SIS-16 score will be summarized by treatment group and time point (30 and 90 days posttroke) for the first poststroke assessment (i.e., this analysis does not account for recurrent strokes).

Differences in the SIS-16 will be compared between each treatment and placebo at each time-point using a linear mixed model. The outcome will be the SIS-16 at each time point (30 and 90 days poststroke). The fixed effects in this model will be treatment, time point (categorical), treatment-by-time point interaction, trial part, and time since index MI (< 6 months, ≥ 6 months). Baseline characteristics that are unbalanced between the treatment groups also will be included in the model. The correlation between measurements within the same stroke (at 30 and 90 days) and between measurements from multiple strokes will be modeled using either random effects or covariance pattern structures.

6.3.5.7 Health care resources utilization, defined as the components of the medical care used by patients in the trial

For endpoint related hospitalizations and data on reason for hospitalization, length of stay, and procedures for diagnostic and therapeutic purposes will be collected. Data on out of protocol physician visits and post-acute care, as well as concomitant medication will also be collected.

Number of hospital admissions for the whole trial

The number of hospital admissions (total and by unit) will be analyzed on the FAS and summarized by treatment group. Treatment groups will be compared based on Negative Binomial regression (Glynn and Buring 1996) with the number of hospital admissions as the dependent variable. The log of time on (prolonged) treatment in years will be used as the offset variable to obtain the point estimate as a rate (number of hospital admissions/number of years in study). The 95% confidence intervals will be provided for the rate ratios (X vs. Y) of hospital admissions. See section 7.2 for details.

Number of days in hospital for the whole trial

Number of days in hospital will also be analyzed on the FAS set and summarized by treatment group. The total number of days in hospital will be calculated as the sum of the days in hospital [including intensive care unit (ICU) days and critical care unit (CCU)] for each individual hospitalized event/admission. For descriptive purposes, the annualized days in hospital, taking into account all hospitalizations with admission date during the double-blind phase, will be calculated for each patient as the number of days of hospitalization divided by total duration of the double-blind phase, then multiplied by 365.25. As described above, the number of days in hospital as the dependent variable will be analyzed and adjusted for treatment duration (log of time on treatment in years will be used as the offset variable) using Negative Binomial regression. The number of days in ICU will also be summarized and analyzed similarly.

In addition to the inferential analysis, descriptive summaries will be presented for the total number of hospital admissions and number of days in hospital for each treatment group.

Sensitivity analysis for hospital admissions and days in hospital

A non-parametric approach will be implemented as a sensitivity analysis for the number of hospital admissions and days in hospital. Patients will be ranked according the following scheme:

1. Patients without hospitalizations will get the "best case" rank
2. For patients who were hospitalized, ranks will be assigned in ascending order of number of hospital admissions (or days in hospital) per patient year.
3. In a second analysis the impact of patient who died will be assessed. Patients who died will get a "worst case" rank with further ranking of the number of hospital admission (days in hospital per patient year as under 2) while the patient was still alive.

The null hypothesis will be tested by assigning ranks on the number of hospital admissions (days in hospital), that a patient had during double-blind phase and then testing the location shift of the medians across the treatment groups. Treatment groups will be compared using the Wilcoxon rank sum test. The significance level for testing treatment differences will be set at the 2-sided 5% level.

6.4 Kaplan-Meier type analyses and graphs

Because this trial has two consecutively recruited trial parts with different allocation ratios that may differ in important predictive covariates and since one treatment group is not even represented in trial part 1, simply pooling data across trial parts to produce an overall Kaplan-Meier graph would not be appropriate. For this reason an alternative approach for producing such a Kaplan-Meier type graph is described in section 6.4.1 below. Such graphs and within any trial part Kaplan-Meier plots will follow the general principles described in section 6.4.2.

Kaplan-Meier type analyses and plots will be provided (including by trial part) for the primary endpoint, key secondary endpoints, secondary endpoints and a selected subset of exploratory outcomes.

6.4.1 Overall Kaplan-Meier type graphs across trial parts

A Cox model stratified for treatment group (placebo, 50 mg, 150 mg or 300 mg) and time since index MI (< 6 months, ≥ 6 months), with trial part as a covariate will be used to obtain Breslow estimates (Breslow 1974) for the predicted survival curves for each combination of treatment group, time since index MI and trial part – including for the 50 mg group in trial part 1. These predicted survival curves will then be aggregated for an appropriate cohort of patients within each of the 4 treatment groups to obtain a single overall Kaplan-Meier type graph for the 4 treatment groups.

The use of a Cox model stratified for treatment group (placebo, 50 mg, 150 mg or 300 mg) – and also time since index MI (< 6 months, ≥ 6 months) – is a suggestion by Zhang et al. (Zhang et al. 2007) and Terry Therneau (personal communication, 2011). As pointed out by Zhang et al. such a model makes no assumption of proportional hazards between treatment groups or time since index MI groups. Thus, it is more appropriate for obtaining a graphical representation that allows an inspection of the relative effectiveness of treatment groups over time. Using trial part as a covariate and assuming the same proportional effect of trial part for the whole follow-up period for each of the 8 strata (treatment group / time since index MI)

allows extrapolation of what a 50 mg group in trial part 1 would have been like, as suggested by Terry Therneau (personal communication, 2011). To assess the assumptions involved the predicted survival curves from this model for the placebo, 150 mg and 300 mg groups in each stratum and for the 50 mg group in all trial part 2 strata will be compared graphically to those from a model that treats trial part as an additional stratification variable. Should the assumption be strongly violated with respect to trial part having a constant effect over time, it would be an alternative to assume a trial part effect that is only proportional over specific time intervals (e.g. up to 90 days, day 91 to day 183, days 184 to 1 year, 1 year to 2 years, > 2 years).

The overall aggregated cohort survival estimate will be obtained from the estimates for each treatment group / time since index MI / trial part combination using the Hakulinen method (Hakulinen 1982). Compared with the more simple Ederer method this is expected to more closely reflect what might have been obtained, if this study had been conducted with 4 treatment arms from the start. The reason is that the follow-up time after which administrative censoring at trial end will occur will differ – by design – between the trial parts (Thomsen et al. 1992) (Therneau and Grambsch 2000, pp. 261-287).

The cohort for which the cumulative failure rate is estimated using the Hakulinen method will be constructed so that within each trial part the distribution of time since index MI and distribution of maximal potential follow-up is the same for each treatment group. To achieve this within each trial part

1. All the patients in all treatment groups and time since index MI strata in that trial part are selected.
2. Their length of follow-up $\mathbf{F_i}$ and time since index MI information is retained.
3. These patients are assumed to be the (identical) hypothetical recruited cohorts for each of the four treatment groups.

Note that the length of follow-up $\mathbf{F_i}$ is taken to be

- for those patients that were censored: the time from randomization to the maximum actual follow-up for CV events (not just for the first event)
- for patients that had a non-fatal version of the endpoint of interest (e.g. non-fatal MI in case of analyzing the primary MACE endpoint) the same approach as for those patients that were censored will be used
- for patients that had a fatal version of the endpoint of interest (e.g. fatal MI in case of analyzing the primary MACE endpoint) the maximum potential follow-up will be used, i.e. the time from randomization to the maximal potential follow-up date, defined to be the analysis cut-off date (see Section 2.3.7).

For each patient **i** let $\mathbf{S_i(t)}$ be the estimated survival curve based on that patient's treatment group, time since index MI and trial part. If patients are ordered from shortest to longest possible follow-up time $\mathbf{F_{(1)}, F_{(2)}, \ldots, F_{(K)}}$, then the Hakulinen estimate (Hakulinen 1982) for the cumulative survival function $\mathbf{S(t)}$ is calculated recursively for any $\mathbf{F(k) < t \leq F(k+1)}$ as

$$\mathbf{S(t) = S(F_{(k)}) \times [\ \Sigma_{i=1,\ldots,n}\ S_i(t) \times 1\{\ F_i > t\ \}\ ] / [\ \Sigma_{j=1,\ldots,n}\ S_j(F_{(k)}) \times 1\{\ F_j > F_{(k)}\ \}\ ]}$$

as described by Thomsen et al. (Thomsen et al. 1992), Nielsen (Nielsen 1997) and Therneau and Grambsch (Therneau and Grambsch 2000, pp. 261-287).

Note that valid confidence intervals cannot be obtained for these estimates in a straightforward fashion, because of the artificially inflated "apparent sample size" resulting from the way in which the algorithm above ensures balanced time since index MI/trial part across treatment groups and censoring patterns. If pointwise confidence intervals are required (e.g. primary and secondary endpoints) one could create e.g. B=2,000 bootstrap samples, repeat the whole process above (starting from fitting the Cox model) for each bootstrap sample and then obtain interval percentile (or BCa) Bootstrap confidence intervals as described by Efron and Tibshirani (Efron and Tibshirani 1993, pp. 170-176 and pp. 184-188) e.g. for times t=1 year, 2 years, 3 years and 4 years. algorithm might be applied.

6.4.2 Kaplan-Meier graphs for each trial part and general principles

The approach for Kaplan-Meier graphs closely follows the recommendations by Pocock et al. (2002).

Cumulative event rate estimates (1 – estimated survivor function) in % versus time of follow-up in years will be shown based on Kaplan-Meier estimates. Compared to showing the survivor function this maximizes detail without needing a break in the scale.

While "technically, any survival plot can be extended right through to the longest follow-up time" as Pocock et al. point out "this extension is not good statistical practice, since for any such plot the eye is drawn to the right (i.e. where the plot finishes), which is where there is least information and greatest uncertainty". Kaplan-Meier curves will therefore only drawn up to the time at which the total population at risk for the event in question has decreased to 10% of the size of the analysis set. This matches the recommendation by Pocock et al. who wrote that they "[..] recommend that survival plots be halted once the proportion of patients free of an event, but still in follow-up, becomes unduly small. […] What constitutes "unduly small" is open to debate and depends on the context. It will often be reasonable to curtail the plot when only around 10–20% are still in follow-up." As CANTOS is a large outcome trial the lower end of this range (10%) will be used.

For the kind of Kaplan-Meier type graphs described in section 6.4.1 above, this will be taken to mean that the graph will be truncated at the length of follow-up achieved by 10% of patients across all trial arms and trial parts. This means that the graph for the 50 mg dose will be continued somewhat past the point up to which 10% of 50 mg patients were followed up.

The number of patients at risk in each group will be displayed below the x-axis at year=0, 1, 2, 3… and each subsequent year of follow-up to provide information on the extent of follow-up. Pointwise 95% confidence intervals at each full year may be shown if feasible. In line with the recommendations by Pocock et al. this provides some measure of statistical uncertainty and ensures that any visual signs of treatment differences do not look more convincing than they really are. Results of inferential statistics (e.g. primary model-based hazard ratios, 95% confidence intervals and p-value for primary endpoint) will also be shown on the figure. Kaplan-Meier tabulations will show number at risk, number failed, cumulative number failed, cumulative number censored, Kaplan-Meier estimates of failure rate with pointwise 95% confidence intervals. Similar tabulations will be provided by time interval also including the estimated hazard at interval midpoint.

It is recognized that just as discussed by Pocock et al. caution is needed in interpreting the shape of survival plots in particular due to the lack of any pre-specified hypothesis about its shape and the lack of statistical power to explore subtleties of treatment difference other than the overall comparison.

6.4.3 Calculation of number needed to treat

The number needed to treat (to benefit) will be calculated using the method of Altman and Andersen (Altman and Andersen 1999) for each dose for different durations of treatment as

$$\mathbf{NNT\ (t) = 1\ /\ [\ S_{placebo}(t)^{\text{hazard ratio for dose versus placebo}} - S_{placebo}(t)\ ]}$$

using S(t) calculated as described in section 6.4.1. It will be extrapolated as described by Altman and Andersen to the 5 year timepoint from the timepoint of follow-up achieved by 10% of patients across all trial arms and trial parts $T_{10\%}$ under the assumption of approximately constant event rates and benefit as

$$\mathbf{NNT\ (5\ years) = (\ T_{10\%}\ /\ 5\ years\ ) \times NNT\ (T_{10\%}).}$$

3 year and 1 year NNTs will be calculated and it is expected that this can be done without such an extrapolation unless the study is stopped an interim analysis. Confidence intervals with appropriate coverage probabilities will be calculated using Bootstrap methods.

6.5 Methodology for dose response evaluation

Dose-response estimation will be performed to support the evaluation of a number of endpoints as indicated in the protocol, among them the hazard ratios derived from the analysis of the primary endpoint.

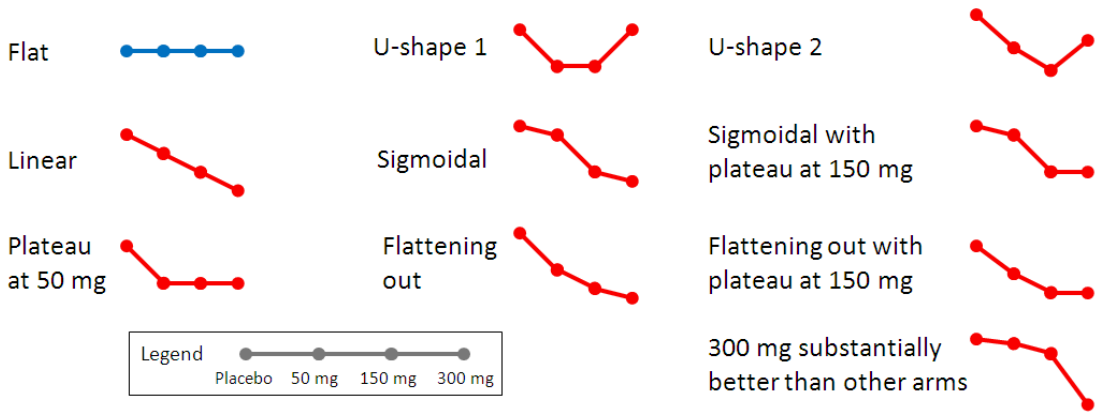
Dose-response estimation will be done using parametric dose-response modelling as described in Pinheiro et al. (2014) combined with model averaging techniques (see Bornkamp et al. 2015). The model averaging approach will use a weighted subset of seven possible parametric models as the estimate of the dose response. The parametric models are a linear model, a quadratic model, a model linear in log dose, an emax model, a sigmoid emax model, an exponential model, and a beta model as implemented in the R package DoseFinding. The model averaged dose response and confidence intervals will be derived from a parametric bootstrap. In addition, comparisons between doses will also be derived with their corresponding confidence intervals.

The time to event endpoints analyzed using the general approach as described in Pinheiro et al. (2014) will use the estimated hazard ratios and covariance matrix derived from a parametric regression model for survival endpoints for which the treatment estimates are given a proportional hazards model. Estimates for the analysis of other endpoints will be derived from fitting models that account for measurements collected over time whenever applicable. Note that the dose response evaluation described here is considered exploratory.

The estimation of the dose response will be based on the methods described in Pinheiro et al. 2014 as a more general framework for the derivation of dose responses when the response is any form of derived statistic for the dose groups with their corresponding variance covariance matrix.The derived dose response will be obtained from a model that is the average of at least three of fitted models of dose response where the weights will used the generalized AIC

measure as described in Pinheiro et al 2014. The corresponding mean dose response curve and its confidence intervals will be derived from a parametric boostrap procedure also described in the same reference.

Figure 6-6 Candidate dose response patterns



7 Safety evaluation

Safety will be evaluated based on the safety set (SAF). The assessment of safety will be based primarily on the assessment of potential and identified risks defined in the risk management plan (RMP), the frequency of adverse events, laboratory abnormalities, and serious adverse events suspected by the investigators to be related to study treatments. Other safety data (like vital signs, ECG) will be summarized as appropriate.

Selected safety analyses will be based on looking at events and variables recorded while patients were still on investigational drug (i.e. data will be considered censored at the latest one quarter year + 28 days = 119 days after the last study injection, and up-to/including the EOS visit of the core phase), as supportive analyses.

Since the study is intended to be the only pivotal trial in the regulatory submission, selected key safety analyses including disposition, demographics, exposure, adverse events, serious adverse events, key outputs for adverse events of special interest, deaths, laboratory abnormalities and laboratory values over time will be repeated for those groups specified in table 2.3-2.

Selected safety analyses will also be shown by time period (from randomization to ≤ 3 months post-randomization, > 3 to ≤ 6 months, > 6 to ≤ 9 months, > 9 to ≤ 12 months, > 12 months to the end of core study visit) to evaluate any changes in safety during more short-term and longer term treatment.

7.1 Safety assessment approach accounting for multiplicity

No adjustments for multiplicity will be made for safety assessments. Adjustments will be made for multiplicity of the primary and key secondary efficacy endpoints, as described earlier in this document.

7.2 Statistical models used in multiple safety contexts

Safety data will be summarized across the two trial parts and the two randomization plans in trial part 2, both of which might influence safety reporting as described in section 2.4.

For this purpose hazard ratios versus placebo will be estimated for binary safety outcomes (e.g. at least one occurrence of adverse events) using Cox regression stratified for time since index MI and trial part. Time to event methods have been chosen over relative risk regression or logistic regression to account for differential follow-up This can be implemented using SAS code similar to the following:

```
proc phreg data=dataset;
  class treatment(ref="Placebo") <time since index MI>
      <trial part>;
  model time*event(0) = treatment / ties=exact risklimits;
 strata <time since index MI > <trial part>;
run;
```

Trial part by treatment interactions will be investigated. For selected events, additional predictive baseline covariates may be added to the model, namely age, sex, race, region and other event specific variables. As summary statistics patients with an event per 100 patient years of follow-up (defined as follow-up to first event or censoring) will be reported.

Rates of multiple occurrences of safety events will be compared between treatment groups for selected safety events of special interest, where such an analysis is of interest. A Negative Binomial regression including terms for treatment, trial part, and log (time at risk) as offset variable will be used. This model was chosen, because the number of recurrent events in a population will follow a negative binomial distribution if there is a distribution of different individual Poisson event rates in the population that follows a gamma distribution (Glynn et al. 1993) (Glynn and Buring 1996). While the population distribution may not exactly follow a gamma distribution, the maximum likelihood estimation of the additional dispersion parameter compared to the Poisson distribution from the data allows the negative binomial model approximate the data in this respect and to capture the extent of unexplained heterogeneity in the population. The logarithm of the time at risk is used as an offset (i.e. as a covariate with coefficient 1), because a log link function is used in order to effectively analyze the rate of events per time unit. The following SAS code illustrates the statistical model and methods intended for this analysis:

```
PROC GENMOD DATA=events;
 CLASS treatment(ref='Placebo') <trial part & time since index MI>;
  MODEL <number of events> = treatment
      <trial part & time since index MI> / OFFSET=<log time at risk>
```

```
        DIST=NB LINK=LOG LRCI;
RUN;
```

As matching summary statistics, events per 100 patient years of follow-up will be reported. For selected events, additional potentially predictive covariates will be added to the model, namely at least age, sex, race and region. When selecting repeated events it has to be ensured that a single adverse event case report form entry is only counted once (e.g. by ensuring only one record per adverse event sequence number is counted), as analysis dataset may contain multiple records for one CRF report to allow identification via e.g. different SMQs.

When such a model is used for specific adverse events of interest and a sufficient number of events to make this display useful is available, these data will also be displayed graphically as events per unit time of follow-up for different time intervals (e.g. first 6 months, 6 months – 1 year, 1 year to 2 years … or smaller time intervals as appropriate) using meaningful categories of time to show time patterns of event occurrence and potential changes in treatment effect over time. Measures of uncertainty will be provided, as well as information on the extent of overdispersion / population heterogeneity.

Changes from baseline in continuous safety parameters will be plotted over time based on both trial parts using repeated measures mixed model. The following SAS code illustrates the statistical model and methods intended for this analysis:

```
proc mixed data=dataset;
  class patient visit treatment <trial part>
      <time since index MI>;
  model <change from baseline> = treatment visit treatment*visit
      baseline <trial part>
      <time since index MI>
      / s ddfm=kr;
  repeated visit / subject = patient type = un;
run;
```

with appropriately transformed values. Comparisons of each dose to placebo at each visit will be conducted if feasible. Additional analyses will add potentially predictive covariates, namely age, sex, race, region, education, exercise level, alcohol use, smoking history, BMI and hypertension to the model. The following variables will be analyzed on the log-scales and results will be back-transformed to report geometric means and ratios of geometric means versus placebo:

- Urine albumin/creatinine ratio, urine albumin, urine creatinine
- ALT (SGPT), AST (SGOT), total bilirubin, direct bilirubin, alkaline phosphatase
- Triglycerides, HDL, LDL, VLDL
- hsCRP

All other safety variables will be analyzed without any transformation based on the arithmetic mean and differences in arithmetic means versus placebo.

Panel plots of the results of these analyses showing means/geometric means or differences in means/ratios of geometric means over time will be made available for the clinical study report. 95% pointwise confidence intervals will be provided to allow judgment on the variability in the underlying data, but due to the obvious multiplicity issues consideration of these confidence intervals or p-values from the model described above cannot form the basis of any formal inference.

7.3 Other safety evaluation

7.3.1 Adverse Events

Adverse events between informed consent and randomization

Adverse events between informed consent and randomization will be summarized by primary system organ class and preferred term for all randomized patients (as opposed to the safety set). This summary will include events that would qualify as trial endpoints if they occurred after randomization, but which are to be reported as AEs prior to randomization.

Serious adverse events occurring after informed consent will be reported for all screened patients, as well as separately for all randomized patients and for screen failures.

Adverse events (AEs) excluding trial endpoints

The incidence of treatment emergent AEs (events started on the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term, up-to/including the earlier date of 119 days after the last study injection or the EOS visit of the core phase) excluding trial endpoints will be summarized by primary system organ class (SOC), preferred term and also by severity and relationship to study treatment. Standardized MedDRA Queries (SMQs) may also be employed. The MedDRA version used for reporting the study will be clearly identified.

Any adverse events reported by the investigator with the onset date after randomization and up-to/including the end of core phase visit and prior to clinical database lock will be included in AE analyses irrespective of how long after last study drug intake. Adverse events occurring after a patient's end of core phase visit will be reported as part of the washout phase/long-term safety extension phase.

If a patient reported more than one AE with the same preferred term, the AE with the greatest severity will be presented. If a patient reported more than one AE within the same primary system organ class, the patient will be counted only once with the greatest severity at the system organ class level, where applicable.

The number and percentage of patients reporting any AE during the double-blind phase of the study will be summarized by primary system organ class, preferred term and treatment. The most common adverse events reported (reported by ≥ 2 % of patients in any group for each preferred term or ≥ 2 % in any group for each SMQ) table will be presented in descending frequency starting from the most common event.

Separate summaries will be provided for AEs suspected by the investigator to be related to study drug, deaths, SAEs, and AEs leading to discontinuation.

Events reported on endpoint pages

The following events reported by investigators on the trial endpoint pages will be summarized by treatment group for safety purposes, because they are as per the study protocol not reported as adverse events (further sub-categorizations may be added as needed):

- All-cause death
  - Non-cardiovascular death
    - Non-cardiovascular death due to accident/trauma
    - Non-cardiovascular death due to respiratory failure
    - Non-cardiovascular death due to infection
    - Non-cardiovascular death due to sepsis
    - Non-cardiovascular death due to malignancy
    - Non-cardiovascular death due to suicide
    - Non-cardiovascular death due to renal failure
    - Non-cardiovascular death due to liver failure
    - Non-cardiovascular death due to other non-vascular reason
  - Cardiovascular death
    - Coronary Heart Disease death
      - Cardiovascular death due to myocardial infarction
      - Cardiovascular death due to congestive heart failure/cardiogenic shock
      - Cardiovascular death directly related to revascularization
      - Cardiovascular death due to arrhythmias
      - Cardiovascular death due to witnessed sudden death
      - Cardiovascular death due to unwitnessed sudden death seen within 24 hours
      - Cardiovascular death (unwitnessed death)
      - Cardiovascular death (death due to unknown cause)
      - Cardiovascular death due to other vascular causes identified as Ischemic Heart Disease (i.e. fulfilling narrow “Ischaemic heart disease” SMQ)
    - Cardiovascular death due to other vascular causes not identified as Ischemic Heart Disease (i.e. not fulfilling narrow “Ischaemic heart disease” SMQ)
    - Cardiovascular death due to atherosclerotic non-coronary vascular disease
    - Cardiovascular death due to pulmonary embolism
    - Cardiovascular death due to stroke
      - Cardiovascular death due to non-hemorrhagic stroke
      - Cardiovascular death due to intracranial hemorrhage
- Stroke or TIA
  - Stroke
    - Non-hemorrhagic cerebral infarction

    - Non-hemorrhagic infarction with hemorrhagic conversion
    - Primary hemorrhagic intracerebral stroke
    - Stroke of uncertain type
  - Transient Ischemic Attack requiring/not requiring hospitalization
- Coronary vessels with >50% stenosis
  - Coronary vessels >50% stenosis: Left Main
  - Coronary vessels >50% stenosis: LAD
  - Coronary vessels >50% stenosis: LCX
  - Coronary vessels >50% stenosis: RCA
  - Coronary vessels >50% stenosis: Bypass Graft
- Myocardial infarction (with 12 sub-classifications as below)
  - Spontaneous myocardial infarction with/without new ST segment elevation with/without new Q waves identified
  - PCI-related myocardial infarction with/without new ST segment elevation with/without new Q waves identified
  - CABG-related myocardial infarction with/without new ST segment elevation with/without new Q waves identified
- Unstable Angina (with 4 sub-classifications as below)
  - Unstable angina requiring/not requiring unplanned revascularization and requiring/not requiring hospitalization
- Coronary revascularization (with 4 sub-classifications as below)
  - Urgent/Elective percutaneous coronary intervention without stenting/using drug eluding stent/bare metal stent/unknown type of stent
  - Urgent/Elective coronary artery bypass graft (1 bypass graft/>=2 bypass grafts)
- Non-coronary revascularization (with 21 sub-classifications as below)
  - Stenting/Surgical revascularization/Other revascularization of carotid artery/aorta/iliac artery/femoral artery/popliteal artery/renal artery/other artery
- Stent thrombosis in a previously stented segment
  - Stent thrombosis in a segment previously stented with a drug eluding stent
  - Stent thrombosis in a segment previously stented with a bare metal stent
  - Stent thrombosis in a segment previously stented with an unknown type of stent
- Hospitalization or prolongation of hospitalization for heart failure
  - Hospitalization or prolongation of hospitalization for heart failure with elevated BNP
  - Hospitalization or prolongation of hospitalization for heart failure with elevated NT-proBNP
  - Hospitalization or prolongation of hospitalization for heart failure with elevated BNP and NT-proBNP
  - Hospitalization or prolongation of hospitalization for heart failure without elevated BNP or NT-proBNP

- Critical limb ischemia (with 16 sub-classifications as below)
  - Critical limb ischemia requiring hospitalization
    - Critical limb ischemia in left lower extremity/left upper extremity/right lower extremity/right upper extremity requiring revascularization/not requiring revascularization and requiring hospitalization
  - Critical limb ischemia not requiring hospitalization
    - Critical limb ischemia in left lower extremity/left upper extremity/right lower extremity/right upper extremity requiring revascularization/not requiring revascularization and not requiring hospitalization
- Limb amputation due to vascular cause (with 10 sub-classifications as below)
  - Amputation of right lower extremity/right above knee amputation/…/left upper extremity
- Deep vein thrombosis (with 14 sub-classifications as below)
  - Deep vein thrombosis in left leg (proximal with calf/proximal without calf/calf only)/right leg (proximal with calf/proximal without calf/calf only)/other limb confirmed by diagnostic study/not confirmed by diagnostic study
- Pulmonary Embolism
  - Pulmonary embolism in left/right lung confirmed/not confirmed by at least one diagnostic study
- Supraventricular tachycardia/Atrial Fibrillation
  - Supraventricular tachycardia
  - Atrial fibrillation
  - Atrial flutter
  - Other arrhythmia
- New onset diabetes
  - New onset diabetes based on start of new diabetes medication
  - New onset diabetes based on laboratory criteria
    - New onset diabetes based on HbA1c only
    - New onset diabetes based on FPG only
    - New onset diabetes based on HbA1c and FPG

7.3.2 Laboratory data

Laboratory values that the laboratory reports to be below or above the limit of quantification will be imputed as 0.5 × and 1.5 × the respective limit of quantification. Should there be a substantial proportion of values below the lower limit of quantification and/or above the upper limit of quantification for an important laboratory parameter (see Table 7-1), the summary statistics (mean, standard deviation) will also be calculated as the maximum likelihood estimates using a parametric model for data that can be right censored and left censored at the upper and lower limit of quantification, respectively, using the following methods

- Arithmetic mean and SD are calculated using PROC LIFEREG assuming a normal distribution

- Geometric mean and CV%(geometric mean) are calculated using PROC LIFEREG assuming a log-normal distribution and back-transformed
- Empirical median will not be calculated in the case of censoring. Empirical minimum will not be calculated if there are values < lower limit of quantification, similarly the empirical maximum if there are values > upper limit of quantification.
- Quartiles from the parametric distribution can also be calculated upon request when Q1, median or Q3 does not lie between the lower and upper limits of quantification.

The summary of laboratory evaluations will be presented for three groups of laboratory tests (Hematology, Serum chemistry and Urinalysis). Summaries will consist of descriptive tables stratified by treatment and time point.

Descriptive summary statistics (mean, median, standard deviation, Min and Max) for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by laboratory test and treatment group. Change from baseline will only be summarized for patients with both baseline and post baseline values and will be calculated as:

change from baseline = post baseline values – baseline value

In addition, shift tables will be provided for all parameters except for creatinine clearance in order to compare a patient's baseline laboratory evaluation relative to the extreme post-baseline value. For the shift tables, the normal laboratory ranges will be used to evaluate whether an extreme post-baseline value was normal, low, or high relative to whether or not the baseline value was normal, low, or high. These summaries will be presented by laboratory test and treatment group.

The frequency and percentage of patients with clinically notable laboratory results after baseline will be tabulated. Clinically notable laboratory results, for those parameters where ranges are available, are given in Table 7-1 below and are based on the FDA Division of Neuropharmacology guidelines. Only patients with laboratory results not notably abnormal at baseline from the central laboratory at baseline will be included in the tabulations.

Table 7-1 Clinical notable criteria for selected laboratory tests

Laboratory parameter (unit)	Lower bound of clinically notable range	Upper bound of clinically notable range
Hematology		
Hematocrit (%)	30	60
Hemoglobin (g/dL)	10	20
Platelet count (x 10^9/L)	100	600
RBC (x 10^{12}/L)	3.3	6.8
WBC (x10^9/L)	3.0	15.0
Basophils (%)	-	6
Eosinophils (%)	-	10
Lymphocytes (%)	10	60
Monocytes (%)	-	20
Absolute neutrophils (x 10^9/L)	1	12
Chemistry		

Laboratory parameter (unit)	Lower bound of clinically notable range	Upper bound of clinically notable range
Albumin (g/L)	25	60
Alkaline Phosphatase (U/L)	-	280
BUN (mmol/L)	0.7	14.3
Calcium (mmol/L)	1.87	2.89
Chloride (mmol/L)	85	119
Creatinine (mcmol/L)	18	221
LDH (U/L)	0	500
Potassium (mmol/L)	3	6
AST (U/L)	-	100
ALT (U/L)	-	110
Total Bilirubin (mcmol/L)	-	43
Total Protein (g/L)	40	95
Uric Acid (mcmol/L)	89	595
BUN/Serum Urea (mmol/L)	0.7	14.3
Sodium (mmol/L)	125	154

Patients' worst CTC classifications as per table 7-2 at any point during the study will also be provided. The number of patients with eGFR declines compared to baseline of ≥ 25%, ≥ 40% or ≥ 50%, or by ≥ 30 ml/min/1.73 m^2 at any point in the study will be summarized as well as those with serum creatinine increases compared to baseline of ≥ 50%, ≥ 0.5 mg/dL, ≥ 2.0 mg/dL, ≥ 2.5 mg/dL or ≥ 3.0 mg/dL.

Time to nephropathy in terms of urine albumin/creatinine ratio (≥ 30 mg/mmol) will be assessed.

Additionally, the occurrence of nephropathy based on selected adverse event groupings as defined in the CRS, doubling of post-baseline serum creatinine in comparison to baseline, endstage renal disease (ESRD) defined as dialysis, renal transplant, or serum creatinine >530 µmol/L (6.0 mg/dL) and time to non-cardiovascular death due to renal failure will also be analyzed. An overall composite will also be provided. The continuous log-transformed urine albumin creatinine ratio will be also analyzed as well as eGFR over time and abnormalities will be considered.

Table 7-2 NIH CTC version 4.0 grades for Chronic kidney disease, which can be assessed in this trial

CTC terms	Grade 1	Grade 2	Grade 3	Grade 4
Chronic kidney disease	eGFR† <LLN - 60 ml/min/1.73 m^2	eGFR† 59 - 30 ml/min/1.73 m^2	eGFR† 29 - 15 ml/min/1.73 m^2	eGFR† <15 ml/min/1.73 m^2; dialysis or renal transplant indicated*

† CrCl not assessed in this study

* in this study to be defined as report of kidney transplant or dialysis as non-drug therapy

7.3.3 Vital signs

Descriptive summary statistics (mean, median, standard deviation, Min, Max) for the change from baseline to each post baseline visit will be presented. These descriptive summaries will be presented by vital sign and treatment group. Change from baseline will only be summarized for patients with both baseline and post-baseline values and will be calculated as:

change from baseline = post-baseline value – baseline value

The frequency and percentage of patients with clinically notable vital signs (based on the worst value in changes from baseline) will be tabulated. Clinically notable vital sign results are provided in Table 7-3 below. Pulse pressure will be derived as systolic – diastolic blood pressure and reported.

Table 7-3 Clinically notable changes in vital signs

Vital Sign (unit)	Clinically notable criteria
Weight (kg)	increase > 10% from Baseline
Systolic blood pressure (mmHg)	≤90 and decrease from baseline of ≥30 or <75
	≥180 and increase from baseline of ≥30 or >200
Diastolic blood pressure (mmHg)	≤50 and decrease from baseline of ≥20 or <40
	≥105 and increase from baseline of ≥20 or >115
Pulse (bpm)	≤50 and decrease from baseline of >30 or <40
	≥120 and increase from baseline of >25 or >130

7.3.4 Electrocardiogram (ECG)

In the CANTOS trial, baseline and yearly thereafter ECGs will be taken; ECG results will be centrally read for changes including QTc changes and silent MIs for clinical CAD endpoints.

The following quantitative variables will be summarized at each visit using standard summary statistics: ventricular rate (heart rate), RR interval, PR interval, QRS duration, QT interval, and corrected QT interval (QTcF/QTcB). The difference between treatment groups in observed values and changes from baseline with associated 95% confidence interval will be provided for each of these criteria. QTc data will be analyzed for both the Fridericia (primary) and Bazzett's (secondary) corrections.

Additionally, the number and proportion of patients with

- QT > 550 ms
- QT > 500 ms
- QTc > 500 ms
- QTc > 480 ms
- QTc > 450 ms
- QTc changes from baseline > 30 ms
- QTc changes from baseline > 60 ms
- PR > 250 s

will be summarized .

In addition, shift tables comparing baseline ECG results (normal, abnormal, not available, total) with the maximum on-study result (normal, abnormal, not available, total) will be provided for each variable.

Newly occurring or worsening abnormalities will also be summarized by treatment group. Results in elderly patients (≥ 65), by gender, in patients with congestive heart failure, elevated baseline QT/QTc intervals (for QT/QTc analyses) and baseline HR <55 bpm will be presented.

7.4 Safety topics of interest

This section outlines the currently planned analyses based on the current safety profiling plan. The safety profiling plan is an evolving document outlining the clinical safety plan at any stage of the clinical development of a compound. Thus, due to the length of the trial the analyses based on potential and identified risks may have to be updated according to new information while the trial is ongoing.

In general, analyses for adverse events of special interest based on a list of search criteria stored in the Novartis Clinical REsearch Documentation and Information system (CREDI). For each DMC any analyses to be included in DMC reports will be communicated to the academic independent statistician. Number of affected subjects and percentage will be provided by treatment arm. Risk ratio and 95% confidence interval will be provided for each dose versus placebo. If unbalances occur, time to first occurrence and number of occurrences will be evaluated, if appropriate and not already pre-specified. Dependent on the risk medical history or baseline characteristics may have to be considered further beyond what is prespecified below.

Table 7-4 summarizes the AEs that will be included in any summaries and analyses of AEs of special interest.

Frequency tables will be presented for each AEs of interest as well as the associated MedDRA Preferred Terms. Additionally, Kaplan-Meier plot will be presented for time-to-first event for each AEs of interest unless otherwise specified.

Table 7-4 List of safety topics of interest

Safety topic
Infections/opportunistic infections
Neutropenia
Thrombocytopenia
Immunogenicity/allergenicity
Malignancies
Hepatic safety
Autoimmunity
Injection site reactions
Disorders of lipoprotein metabolism
Vertigo/dizziness
Hypoglycemia

7.4.1 Infections / opportunistic infections

Infections as adjudicated will be summarized based on the adjudicated information including whether the infection was classified as opportunistic, whether the infection was typical or atypical based on the patient's medical history, response to standard antibiotic therapy, whether it was a chronic recurrent infection/exacerbation of a previous infection and the presence of risk factors for infections.

The analyses below will be conducted separately for each of the followings if feasible

- Adjudication committee confirmed infections
- All investigator reported AEs of infection (independent of adjudication)
- All investigator reported SAEs of infection (independent of adjudication)

Additionally, all investigator reported infections will be identified using a list of search criteria in the CRS which will be stored in CREDI. The occurrence of such events will be reported by MedDRA preferred term.

These will be classified by severity, seriousness, whether intravenous antibiotics were required (report of use of i.v. antibiotic as a concomitant medication), whether infection AEs/SAEs were suspected to be related to study drug by the investigator and whether study drug was discontinued due to infections. Non-cardiovascular death due to infection/sepsis will also be analyzed. Time to first infection will also be analyzed both in a stratified Cox regression model, as well as using Kaplan-Meier type analyses.

Since infections are expected to be sufficiently frequent in a long-term study to allow the use of multiple covariates, age, sex, race, and region will be added to the Cox regression models stratified by time to index MI and trial part.

The following analyses will also be presented by time period (from randomization to $\leq$ 3 months post-randomization, > 3 to $\leq$ 6 months, > 6 to $\leq$ 9 months, > 9 to $\leq$ 12 months, > 12 to $\leq$ 18 months, > 18 to $\leq$ 24 months, > 24 to $\leq$ 30 months and so on in 6 month intervals for as long as at least 15% of the trial population are still at risk:

- The number of patients at risk, the number of patients with the specified event, and %
- Annualized event rate (AER) with associated 95% CI. The annualized event rate (AER) is calculated as the total number of patients with specific event divided by the cumulative exposure of time to the first specified events.

Rates of infections including repeated infections will also be presented graphically using a non-parametric estimator of the mean cumulative function, analogous to the Nelson-Aalen estimator of the cumulative hazard function (Johnston and So (2003)) and will be summarized including graphs of infections in different time periods. The following time intervals will be used: from randomization to $\leq$ 3 months post-randomization, > 3 to $\leq$ 6 months, > 6 to $\leq$ 9 months, > 9 to $\leq$ 12 months, > 12 to $\leq$ 18 months, > 18 to $\leq$ 24 months, > 24 to $\leq$ 30 months and so on in 6 month intervals for as long as at least 15% of the trial population are still at risk.

Inferential analysis of the rate of infections will use a negative binomial regression model as described in section 7.2. It will be ascertained by the use of time-dependent period variables whether any potential treatment differences become larger over time, as well as testing for the

interaction of log(time) and treatment. This will be done using a negative binomial model with SAS code similar to the following or equivalent code in another programming language such as R:

```
PROC GENMOD DATA=events;
 CLASS treatment(ref='Placebo') <trial part & time since index MI>
      <time period> sex race region;
  MODEL <number of events> =
      treatment <time period> treatment*<time period>
      <trial part & time since index MI>
      age sex race region / DIST=NB LINK=LOG LRCI
      OFFSET=<log time at risk in time period> ;
  REPEATED SUBJECT=patient / TYPE=UNSTR WITHINSUBJECT=<time period>;
RUN;
```

Time to first infection will be analyzed by each of eight subgroups that might be at higher risk (e.g. elderly patients, diabetic status, patients with low baseline neutrophil counts, current smokers history, obese patients, region, asthma patients, and COPD patients), see definitions in Table 7-5. This will be done in separate stratified cox models for each subgroup, with treatment, subgroup, and treatment*subgroup as covariates.

Table 7-5 Higher Risk Subgroups

Elderly	>=65 years (yes/no)
Diabetics	based on diabetics definition in Table 2.3-1 (yes/no)
Low baseline neutrophils	CTC >=3 at baseline (yes/no)
Current smokers	Current smokers (yes/no)
Obese patients	BMI >=35kg/m^2 at baseline (yes/no)
Regions	The same as above in Table 2.3-1
Asthma patients	PT=”Asthma” in MH (yes/no)
COPD patients	PT=”COPD” in MH (yes/no)

It will be explored whether any potential risk of infections changes based on whether patients have reported a vaccination within 3 months from/including baseline (yes/no), by modelling the time to first infection including treatment, subgroup (vaccination within 3 months, yes/no), and treatment*subgroup. This analysis will also be done for the 6 month time frame (yes/no - live vaccination within 6 months from/including baseline).It should be noted that live vaccinations within 3 months were not permitted in this study.

Separate summaries of infections and tuberculosis related adverse events (defined by HLTs "Tuberculous infections" and "Mycobacteria identification and serology") will be produced for the patients who had tuberculosis, latent or suspected tuberculosis at the start of the study and received randomized study medication. A patients' listing will be provided.

Duration of infections

To investigate whether the duration of infections is affected by canakinumab, duration will be summarized for each of the endpoints below:

- Mean of the durations in days for each patient
- Maximum of the durations in days for each patient
- Proportion of total durations of infections over total duration of follow-up for each patient

7.4.2 Hepatic safety data

Presentation of hepatic safety data will follow the internal Novartis standards for hepatic safety analyses. The risk of liver toxicities will be quantified and described in terms of onset, dose, duration and severity.

Hepatic effects (LFT abnormality) will be identified with selected adverse events (as defined in the CRS), and the laboratory parameters mainly AST (aspartate aminotransferase; also known as SGOT), ALT (alanine aminotransferase; also known as SGPT), ALP (alkaline phosphatase) and TBL (total bilirubin; conjugated (direct) (DBL) and unconjugated (indirect) bilirubin).

All analyses (whether e.g. Cox regression, analysis of covariance or ordinal regression) will take into account baseline log ALT, log AST, log TBL, log direct bilirubin values (only if available in all patients), alcohol use, age, sex, race and region as long as the number of events allows it.

All analyses, when possible, will be performed with baseline glycemic status as a subgroup and including a treatment by baseline subgroup interaction and repeated with abnormal LFTs at baseline as a subgroup including a treatment by baseline subgroup interaction.

Criterion-based "event" tables

Threshold values of interest for liver function tests are given below.

Table 7-6 Hepatic events

Parameter	Criterion
ALT	>3xULN; >5xULN; >8xULN; >10xULN
AST	>3xULN; >5xULN; >8xULN; >10xULN
ALT or AST	>3xULN; >5xULN; >8xULN; >10xULN
TBL	>1.5xULN; >2xULN
DBL	>1.5xULN; >2xULN
TBL and DBL	TBL>1.5xULN+(DBL>ULN,>1.5xULN or >2xULN)
	TBL>2x ULN+(DBL>ULN, >1.5xULN or >2xULN)
ALP	>2xULN; >3xULN
(ALT or AST) & (TBL or DBL)	ALT or AST >3xULN & TBL or DBL >2xULN
	ALT or AST >5xULN & TBL or DBL >2xULN
	ALT or AST >10xULN & TBL or DBL >2xULN

Parameter	Criterion
ALP & (TBL or DBL)	ALP >3xULN & TBL or DBL >2xULN
(ALT or AST) & (TBL or DBL) & ALP	AT >3xULN & TBL or DBL > 2xULN & ALP < 2xULN (potential Hy's Law case) Note: elevated ALP may suggest obstruction as a consequence of gall bladder or bile duct disease; ALP may also be increased in malignancy. FDA therefore terms Hy's Law cases as indicators of pure hepatocellular injury. This does not mean that cases of AT >3xULN & TBL >2xULN & ALP ≥ 2xULN may not result in severe drug-induced liver injury (DILI).

AST = Aspartate aminotransferase; also known as SGOT, ALT = Alanine aminotransferase; also known as SGPT, ALP = Alkaline phosphatase, TBL = Total bilirubin, DBL = conjugated (direct) bilirubin

The laboratory results meeting specified criteria standard table will be used to provide the number and percentage of patients having AST, ALT > 3, 5, 8, 10 x ULN or TBL >1.5, 2 x ULN or ALP > 2, 3 x ULN.

The number and percentage of potential Hy's Law cases will be presented by treatment group. Potential Hy's Law cases are defined as those patients with AST, ALT >3xULN & TBL >2xULN & ALP <2xULN at the same lab measurement.

Shift-tables

A cross-tabulation of baseline and worst post-baseline values by below, within and above normal range categories will be provided. Shift tables will be provided for the parameters AST, ALT, TBL, direct bilirubin and ALP. These summaries will be presented by laboratory test and treatment group.

Standard laboratory change from baseline tables

The lab standard tables will be produced on all the laboratory parameters including changes from baseline in liver parameters. Continuous liver function test values will be plotted over time and analyses of covariance adjusting for covariates will also be performed.

Adverse event tables

Selected groupings (e.g., SMQ, HLGT, HLT) of adverse events, as defined in the CRS will be presented including the respective preferred term frequencies.

Notable events may be defined as liver-related death (Non-cardiovascular death due to liver failure); liver transplantation (from the SAEs and AEs); liver-related study drug discontinuation (from the AEs); any of the 3 events.

The relative risk of the selected groupings (e.g., SMQ, HLT, HLGT) on each of the active treatment dosages relative to control will be calculated with 95% confidence intervals.

The number and percentage of patients with selected groupings of adverse events will be presented.

Graphical displays

For all patients with liver values (AST, ALT, ALP, TBL) matching the thresholds of 5xULN and Hy's Law (Table 7-6), single patient LFT profile graphs will be generated showing all AST, ALT, ALP, TBL lab values reported for this study and the time of study treatment for these patients. An evaluation of Drug Induced Serious Hepatotoxicity (eDISH) plot will also be created.

7.4.3 Malignancy

Occurrence of malignancies as adjudicated by the blinded adjudication committee will be summarized based on whether they are

- Primary type (by MedDRA high level group term/high level term including secondary paths and preferred terms)
- Newly detected or represent an existing malignancy
- Whether the patient's history includes this malignancy
- Evidence of metastases and their stage
- Whether the presentation was considered typical or atypical
- Whether and which risk factors there were
- Whether the malignancy was considered unusual and was the response to therapy as expected.

Malignancies from adverse event reports will be identified using the list of search criteria in the CRS. They will be reported as part of the safety analyses described in section 7.3.1. Preferred terms will be reported to allow assessment of the occurrence of malignancies by site.

The analyses discussed below will be performed separately based on the CEC confirmed malignancies, the investigator reported AEs of malignancies, and the investigator reported SAEs of malignancies, if feasible. Time-to-event analyses will be conducted and Kaplan-Meier type plots will be presented. This will also be done for non-cardiovascular deaths due to malignancy.

To assess whether there is an imbalance when follow-up becomes longer, time-to-first event will be explored looking at <= 2 years of follow-up versus >2 years of follow-up, separately. This will be explored in a Cox regression model including treatment, follow-up (<= 2 years or > 2 years) and the interaction term as covariates.

Following analyses will also be presented by time period (from randomization to $\leq$ 3 months post-randomization, > 3 to $\leq$ 6 months, > 6 to $\leq$ 9 months, > 9 to $\leq$ 12 months, > 12 to $\leq$ 18 months, > 18 to $\leq$ 24 months, > 24 to $\leq$ 30 months and so on in 6 month intervals for as long as at least 15% of the trial population are still at risk.

- The number of patients at risk, the number of patients with the specified event, and %
- Annualized event rate (AER) with associated 95% CI. The annualized event rate (AER) is calculated as the total number of patients with specific event divided by the cumulative exposure of time to the first specified events.

7.4.4 Thrombocytopenia

Effects with respect to thrombocytopenia will be assessed by the laboratory analyses described in section 7.3.2, additionally criteria for decreased platelet counts per CTC grades as shown in table 7-7 will be reported and baseline platelet counts will be taken into account in this analysis. Shifts versus baseline will also be shown per CTC grade.

Table 7-7 NIH CTC version 4.0 grades for platelets

CTC terms	Grade 1	Grade 2	Grade 3	Grade 4
Platelet count decreased	<LLN-75,000/mm^3; <LLN-75.0 x 10^9/L	<75,000-50,000/mm^3; <75.0 - 50.0 x 10^9/L	<50,000 - 25,000/ mm^3; <50.0 - 25.0 x 10^9/L	<25,000/mm^3; <25.0 x 10^9/L

The occurrence of the groupings of adverse events will be analyzed using Cox regression as described in section 7.2 also adding the baseline platelet count to the model and looking for an interaction with treatment.

The baseline use of antithrombotic medications will be evaluated as a subgroup and treatment by subgroup interactions will be evaluated for both the occurrence thrombocytopenia (AE of special interest) and bleeding events (Haemorrhages SMQ), using Cox regression.

Time to the 1st-occurrence of CTC grades ≥3, and time to the 1st-occurrence of bleeding events will be plotted over time using Kaplan-Meier type graphs. A negative binomial regression, as described in section 7.2, will be used to analyze the occurrence of the bleeding events over time. A repeated measures analysis will be performed on the continuous platelet counts change from baseline with the following factors/covariates: treatment, time, time by treatment interaction, time since index MI, randomization plan, and baseline platelet count. Platelet counts change from baseline will also be plotted over time.

7.4.5 Neutropenia

Drug effects on neutrophils will be assessed by the laboratory analyses described in section 7.3.2, additionally decreased neutrophil counts (occurrence of neutropenia) per CTC grades as shown in table 7-8 will be reported and baseline neutrophil / white blood cell counts will be taken into account in this analysis. Shifts versus baseline will also be shown per CTC grade.

Whether baseline neutropenia or early drops in neutrophil counts (or neutropenia) are indicative of infections (defined using adjudicated events of infection, investigator reported infections, and AEs of special interest) will be explored in two separate Cox regression models; one including treatment, baseline neutropenia and the interaction term as covariates, and the second model including treatment, early drops in neutrophil counts (or neutropenia) and the interaction term as a covariate. There are two definitions for the early drop in neutrophil counts (or neutropenia) subgroup, one using an ordinal variable and one using percentage change from baseline, and these are both computed at visits 3 and 4, see Table 2.3-3. There will therefore be four models for this endpoint and these will be displayed in the same table.

Table 7-8 NIH CTC version 4.0 grades for neutrophils

CTC terms	Grade 1	Grade 2	Grade 3	Grade 4
Neutrophil count	<LLN - 1500/mm^3;	<1500 - 1000/mm^3;	<1000 - 500/mm^3;	<500/mm3; <0.5 x

CTC terms	Grade 1	Grade 2	Grade 3	Grade 4
decreased	<LLN - 1.5 x 10^9/L	<1.5 - 1.0 x 10^9/L	<1.0 - 0.5 x 10^9/L	10^9/L

Whether neutrophil differences change over time will be assessed graphically, as well as using a repeated measures analysis of the continuous neutrophil count change from baseline with the covariates: treatment, time, time by treatment interaction, time since index MI, randomization plan, and baseline neutrophil count. Whether the occurrence of abnormalities (especially CTC grade ≥ 3) depends on the potential risk factor baseline neutrophil counts will be investigated using a cox regression model with time to first occurrence of abnormalities (CTC grade ≥ 3) with treatment, baseline neutrophil counts and treatment by baseline neutrophil counts interaction.

The number of patients that discontinued treatment and then returned to normal values or did not return to normal values, as well as those that did not discontinue and then returned to normal values or did not return to normal values will be summarized. The usage of concomitant medications given to normalize white blood cells counts/neutrophil counts will be summarized.

7.4.6 Immunogenicity/allergenicity

Immunogenicity/allergenicity adverse events will be identified using a list of search criteria in the CRS. These adverse events will be looked at overall and only looking at adverse events within 7 days following each subcutaneous injection as well as by severity and seriousness.

Additionally, the number (%) of patients with positive anti-canakinumab antibodies at baseline and post-baseline will be reported and it will be explored whether the occurrence of positive anti-canakinumab antibodies is associated with subsequent immunogenicity/allergenicity adverse events. As up to three scheduled post-baseline immunogenicity assessments are foreseen (month 12, 24 and end of study visit), it will be assessed whether positive results persist at the next scheduled assessments or were transient. Whether hsCRP response in those with positive anti-canakinumab antibodies differs from those without positive anti-bodies will be explored.

7.4.7 Disorders of lipoprotein metabolism

Drug effects on lipids will be assessed by the laboratory analyses described in section 7.3.2. Additional subgroups based on the use of lipid-lowering medications (including classes of these such as statins and fibrates) at baseline will be investigated. CV outcomes are the primary endpoint of this study and sub-group analyses for CV outcomes by baseline lipid values are planned (see section 2.2). Additionally, the dose of statins used will be tracked as described in section 5. The incidence of adverse events such as myopathy that could result from different statin usage patterns may be explored based on the findings. The number of patients with persistently elevated triglycerides (>50% of visits with TG > 500 mg/dL), as well as the occurrence of adverse events such as pancreatitis (acute pancreatitis SMQ) that could result from persistent elevations will be summarized.

7.4.8 Hypoglycemia

As per the draft FDA requirements for the evaluation of prevention of diabetes, rates of hypoglycemia will be compared statistically between groups. Hypoglycemic events will be identified using the the SMQ Hypoglycaemia. Comparisons between treatment groups will be both done as time to first event analyses (including reporting the number of affected patients), as well as analyzing count data (number of patients with a certain number of hypoglycemic episodes – i.e. none, 1 episode, 2 episodes etc.) using negative binomial regression as described in section 7.2. Baseline glucose and HbA1c values will be used as covariates in analyses.

Such reporting will be done for all hypoglycemic events as well as for events classified as severe by the investigator and events classified by the investigator as SAEs.

7.4.9 Autoimmunity

Autoimmunity reactions will be described including severity and seriousness, as well as occurrence at ANA antibodies by the end of the study.

7.4.10 Injection site reactions

Events of injection site reactions including including SAEs and those reactions leading to drug discontinuation will be summarized by treatment group and presenting both the frequency and the severity of the events.

7.4.11 Vertigo/dizziness

Events of vertigo and dizziness will be summarized by treatment group and presenting both the frequency and the severity of the events.

7.4.12 Other safety topics

The following safety topics will be identified using a list of search criteria in the CRS unless specified otherwise.

- Routine risk of QT prolongation will be evaluated as described in section 7.3.4.
- Increased uric acid levels will be assessed by the laboratory analyses described in section 7.3.2.
- Long term effects on on kidney function will be assessed by the laboratory analyses described in section 7.3.2.
- Interactions with vaccines will be assessed separately by drug interactions.

8 Interim analyses

Interim analyses of efficacy, futility and safety will be carried out during the study. Two interim analyses of efficacy will be performed when about 50% of the target number of primary cardiovascular events have been accumulated and the second one when 75% of the planned number of events are available. Criteria for the interim and final analyses will be determined using a fixed Bonferroni split of the alpha allocated to the interim analyses and to the final analyses in order to protect the overall one-sided familywise type I error rate across

all analyses at 2.5%. The fixed total one-sided alpha allocated to both interim analyses of efficacy combined is 0.05%. Of this 0.01% is allocated to the first efficacy interim analysis and 0.04% allocated to the second efficacy interim analysis. The one-sided significance level for the final analysis is thus 2.45%.

Interim analyses for futility will be conducted simultaneously with the two analyses of efficacy. It should be noted that the efficacy criteria are not modified to "buy back" alpha based upon the presence of futility boundaries; this conservative approach ensures that the familywise type I error rate of the study is protected.

Full details on boundaries and stopping rules will be pre-specified in the Charter of the Data Monitoring Committee (DMC). Timing and number of safety analyses will also be specified in DMC charter.

Protocol amendment 8 introduced an additional early futility analysis to be performed at approximately 30% of the target number of 1400 patients have experienced CEC confirmed MACE. The analysis plan of the early futility was discussed in a separate document. No multiplicity adjustment will be made for the additional early futility analysis, because it will not result in rejecting a null hypothesis for efficacy superiority.

Interim analysis will be performed by an independent academic statistical data analysis center at Brigham and Women's Hospital (Massachusetts, USA) external to Novartis, who will not be involved in the trial conduct. The results will be reviewed by the Data Monitoring Committee (DMC).

Investigators, Novartis employees and others who are involved in the conduct of the trial and in the analysis of the final trial results, or who have contact with study centers, will remain blinded to the treatment codes and interim analysis results until all monitoring decisions have been made and the database has been locked for final analysis.

DMC

In CACZ885M2301, a DMC will monitor the trial's progress, safety and efficacy on a regular basis or per the request of the DMC. Details regarding the reasons for the DMC and the grounds for stopping/continuing trials, as well as the DMC procedures are provided in the DMC charter.

9 Sample size and power considerations

Sample size and power considerations are addressed in section 9.6 and 9.7 of the clinical trial protocol.

Appendix 1: Post-stroke functional assessment sub-study

Full details of the planned analyses for the Stroke Functional Assessment Sub-study, will be specified separately, prior to completion of the first Interim analysis.

In line with the primary objective of the post-stroke functional assessment sub-study to evaluate whether canakinumab arms facilitate functional recovery from stroke, the primary endpoint for this sub-study is the modified Rankin scale assessment 90 days post-stroke.

Further endpoints are the 30 day results of the modified Rankin scale assessment, the 30 and 90 day MFSI-SF and the 30 and 90 day SIS-16.

Note that while patients were initially randomly assigned to treatments, the subset of patients experiencing a stroke may represent a biased subset. The impact of the occurrence of fatal strokes in the main study on the results of the sub-study also needs to be considered.

Besides basic summary statistics the main study report will report an intention-to-treat analysis that will rank patients from best to worse as

- alive at trial end and no stroke,
- alive at trial end and stroke with best Rankin scale (similarly also MFSI-SF/SIS-16)
- alive at trial end and stroke with worst Rankin scale (similarly also MFSI-SF/SIS-16)
- dead at trial end

Ranking within these categories will be done with earlier stroke/death being worse than a stroke/death occurring later.

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