EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 October 2013
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Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment Report

Simponi (golimumab)

EMEA/H/C/000992/X/0047

Applicant: Janssen Biologics B.V., Einsteinweg 101 NL-2333 CB Leiden, the Netherlands

Note

Day 120 Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Janssen Biotech, Inc.
Exhibit 2052
Accord v. Janssen
IPR2026-00258
Ex. 2052-001

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Administrative information

Invented name of the medicinal product:	**Simponi**
INN (or common name) of the active substance(s):	golimumab
Applicant:	Janssen Biologics B.V., Einsteinweg 101 NL-2333 CB Leiden, the Netherlands
Applied Indication(s):	Rhe *Rheumatoid arthritis (RA)* *Simponi, in combination with methotrexate (MTX), is indicated for:* *- the treatment of moderate to severe, active rheumatoid arthritis in adults when the response to disease-modifying anti-rheumatic drug (DMARD) therapy including MTX has been inadequate.* *Simponi, in combination with MTX, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.*
Pharmaco-therapeutic group (ATC Code):	L04AB06
Pharmaceutical form(s) and strength(s):	Solution for infusion 12.5 mg/ml

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List of abbreviations

ACR American College of Rheumatology
ADR adverse drug reactions
AE adverse event
ALT alanine aminotransferase
ARA American Rheumatism Association
AS ankylosing spondylitis
AST aspartate aminotransferase
ATC Anatomical Therapeutic Chemical
CCP cyclic citrullinated peptide
CFR Code of Federal Regulations
CHF congestive heart failure
CI confidence interval
CL Total systemic clearance of drug after intravenous administration
CRP C-reactive protein
CSR Clinical Study Report
DAS28 disease activity score
DBL database lock
DMARD disease-modifying antirheumatic drugs
ECLIA electrochemiluminescent immunoassay
EIA enzyme immunoassay
EQ-5D EuroQol-5D
EU European Union
FACIT-Fatigue Functional Assessment of Chronic Illness Therapy-Fatigue
FDA Food and Drug Administration
FVP final vialed product
GCP Good Clinical Practices
HAQ Health Assessment Questionnaire
HBV Hepatitis B virus
ICH International Conference on Harmonisation
IgG immunoglobulin G
IL interleukin
ITT intent-to-treat
IV Intravenous
IVRS interactive voice response system
LLOQ lower limit of quantification
MAA Marketing Authorization Application
MAH Marketing Authorization Holder
MCS mental component summary
MedDRA Medical Dictionary for Regulatory Activities
MPA Medical Products Agency
MTX methotrexate
NSAID nonsteroidal anti-inflammatory drug
PCS physical component summary
PFS pre-filled syringe
PK pharmacokinetic(s)
PsA psoriatic arthritis
PSUR Periodic Safety Update Report
Q inter-compartmental clearance
q4w every 4 weeks
q8w every 8 weeks
q12w every 12 weeks
QOL quality of life
RA rheumatoid arthritis
RF rheumatoid factor
RMP Risk Management Plan
SAE serious adverse event
SAP Statistical Analysis Plan
SC Subcutaneous
SCE Summary of Clinical Efficacy
SCP Summary of Clinical Pharmacology

Ex. 2052-004

SCS Summary of Clinical Safety
SF-36 36-item short form health survey
SmPC Summary of Product Characteristics
TB tuberculosis
TNFα tumor necrosis factor α
ULN upper level of normal
US United States
V volume of distribution
V2 peripheral volume of distribution
vdH-S van der Heijde Modified Sharp
VAS Visual Analogue Scale (Score)

Ex. 2052-005

1. Recommendations

Based on the review of the data on quality, safety and efficacy, the CHMP considers that the application for Simponi, in the treatment of rheumatoid arthritis, is not approvable since major objections still remain, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the preliminary list of outstanding issues (Section 6).

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

- The benefit risk balance is currently negative. The uncertainties with respect to long term safety due to the higher exposure to golimumab after IV administration compared to SC administration are not considered to be outweighed by the rather limited benefits. Thus, a positive benefit/risk balance for the IV formulation needs further justification.

Questions to be posed to additional experts

Inspection issues

GMP inspection(s)

None

GCP inspection(s)

None

New active Substance status

None

2. Executive summary

2.1. Problem statement

TNFα is considered a key inflammatory mediator that exhibits a wide variety of functional activities. Abnormally high levels of TNFα have been implicated in the pathophysiology of several immune-mediated diseases, including rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS). Binding of TNFα by an anti-TNFα antibody prevents the target from binding to cell surface TNFα receptors, and consequently prevents downstream signaling cascades and the deleterious effects of inappropriate or excessive TNFα expression.

Treatment of these rheumatologic disorders with anti-TNFα agents, including SC Simponi, is well established. The MAH states that *"IV golimumab, with its less frequent dosing necessitating fewer office visits, provides an important treatment option to those patients who have difficulty performing self-injection and cannot get help from family members, healthcare professionals or other caregivers to administer the SC treatment at home."*

Ex. 2052-006

With the current application, safety and efficacy data from study CNTO148ART3001 has been provided, and the MAH has compared safety data from an RA SC study with safety data provided from study ART 3001. Also, a document addressing patient categories who would benefit from IV Simponi has been submitted.

A PK modelling investigating safety profiles at different quartiles of exposure has been provided, which is mainly assessed in the PK AR.

An open-label study (P06129) has been included in order to provide data for switching SC to IV/SC.

2.2. About the product

Golimumab is a human monoclonal antibody with an immunoglobulin G (IgG) 1 heavy chain isotype (G1m [1,17] allotype) and a kappa light chain isotype. Golimumab binds with high affinity to both soluble and transmembrane forms of tumor necrosis factor alpha (TNFα) and inhibits TNFα bioactivity. Golimumab is classified according to the Anatomical Therapeutic Chemical (ATC) Classification System as a TNFα inhibitor (ATC code: L04AB06). Other members of this therapeutic class include infliximab, etanercept, adalimumab, and certolizumab pegol.

2.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH has discussed the i.v. development program with the Medical Products Agency (MPA; Rapporteur) and Food and Drug Administration (FDA). No CHMP scientific advice has been given.

2.4. General comments on compliance with GMP, GLP, GCP

2.5. Type of application and other comments on the submitted dossier

This is an application in the centralised procedure (according to Regulation (EC) No 726/2004), Article 3(1), Annex (1) Biotech medicinal product.

- change or addition of a new pharmaceutical form
- change or addition of a new route of administration

Article 8 of the paediatric regulation applies to this application.

3. Scientific overview and discussion

3.1. Quality aspects

Drug substance

The golimumab drug substance used for the manufacture of the SIMPONI FVP(IV) will be manufactured and tested according to the currently approved license.

Drug Product

The final vialed product (FVP) for intravenous infusion (IV) drug product (DP) is supplied as a sterile solution in a single-use, 4-mL Type I glass vial with an elastomeric closure, a aluminum seal, and a dark blue plastic flip-off cap. The FVP (IV) formulation is composed of 12.5 mg/mL golimumab, L-histidine, sorbitol, and polysorbate 80 (PS 80), at pH 5.5. FVP (IV) is manufactured in one presentation: 50 mg/vial (nominal 4.0 mL fill volume).Thus, the newly developed FVP(IV) presentation contains the

Ex. 2052-007

same amount of drug substance as the currently approved PFS presentation (50 mg/0.5 ml) product but is formulated in a lower strength.

The development of the liquid formulation used in FVP (IV) DP was based on experience gained in development and commercialization of the pre-filled syringe (PFS) DP which is used for subcutaneous administration of golimumab. The major differences between FVP (IV) DP and PFS DP are the concentration of the active ingredient and the primary packaging.

The same design process will be used for production of the FVP presentation as is approved for production of DP, prefilled syringe. The description of the production process is given in sufficient detail.

The studies for validation of the production of the intravenous presentation reported in the dossier were performed before both the currently, and the previously, approved specifications for control of drug substance and drug product (PFS 50 mg) were in place. The Applicant will, however, present supplementary data in the response to the Day 120 LoQ, covering production of Simponi FVP (IV) qualification batches and where the drug substance batches used for production have been manufactured under the control strategy approved in the variation procedure EMEA/H/C/0992/37. Production will be carried out in the full commercial scale and the reported documentation will include release, in-process, and characterization data on the qualification batches.

The release and shelf-life specifications for the FVP and PFS presentations include control for the same parameters, where applicable, and share in most cases the same acceptance criteria. The application of the same specifications as approved for PFS is considered satisfactorily justified.

The stability data presented cover the one year shelf-life requested but so far no data are available from studies on the stability of product produced using the proposed process when controlled by the proposed specifications. Supporting comparable stability profile and, thereby also, the application of the same shelf life/shelf-life specifications as is approved for the PFS presentation, the Applicant has committed to place two FVP qualification batches on stability. According to the Applicant, three months data will be available in time for the submission of the response to the Day 120 LoQ, and the six months data at Day 181. The six months stability data, covering only three time points, is considered to represent the minimum amount of data needed for assessment of trends.

Although the request for further documentation has been iterated in several variation or line extension procedures, the information on the statistical model used for evaluation of stability data is still too brief to allow assessment of if the model is valid for the analysis of pooled data. As the MAH makes no claims on e.g. shelf life based on the use of the quadratic model, the concern on the applicability of the model is not further pursued within the current procedure.

3.2. Non clinical aspects

No new data.

3.3. Clinical aspects

Pharmacokinetics

The pharmacokinetics of golimumab was assessed in depth in the original application in 2009. The focus of the current report will therefore be on the new formulation and exposure comparisons between the subcutaneous (SC) formulation and the intravenous (IV) formulation, as well as pharmacokinetics (PK) as a tool in dosing schedule selection.

Pharmacokinetic data related to the intravenous administration of golimumab is available from three Phase 1 studies (C0466T01, C0524T14, and C0524T15) and two Phase 3 studies (C0524T12 and

Ex. 2052-008

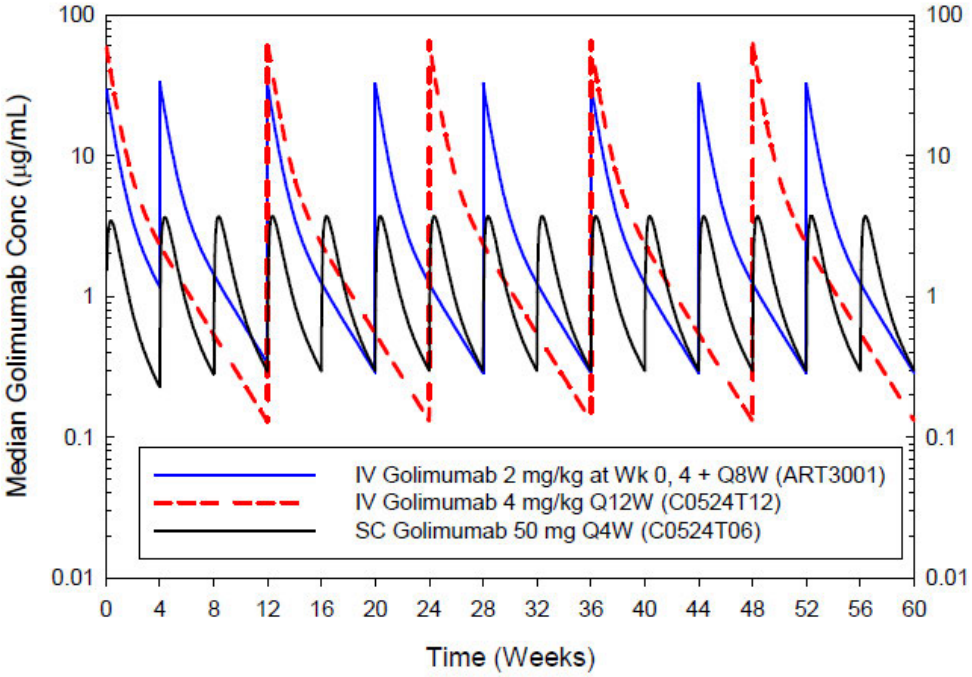
CNTO148ART3001). The clinical pharmacology data from the two Phase 3 studies of IV golimumab (C0524T12 and CNTO148ART3001) in rheumatoid arthritis (RA) subjects represent new information in this application for the treatment of RA by IV golimumab. The data from the three Phase 1 studies were previously submitted in prior submissions.

Furthermore, a population PK analysis was performed. The objectives of the population PK modeling analysis were to develop a population model to characterize the PK of golimumab, and to investigate the effects of covariates on various PK parameters of golimumab following IV administration of golimumab. The population mean estimate for CL (0.6 L/day) from the population PK analysis was similar to the mean values: 0.6 L/day (RA subjects in C0524T14) and 0.5 L/day (healthy subjects in C0524T15) calculated by non-compartmental analysis.

In the purpose of trying to reach drug levels close to or above the trough serum golimumab concentrations resulting from SC golimumab 50 mg q4w, the Applicant has used the PK results from CNTO148ART3001 and C0524T12 (IV dosing) and the results from study C0524T06 (SC dosing) for simulations.

The simulation results showed that an IV dosing regimen of golimumab 2 mg/kg q8w resulted in a median trough steady-state golimumab concentration of 0.28 µg/mL; while an SC dosing regimen of golimumab 50 mg q4w produced a median steady-state trough concentration of 0.30 µg/mL. After adjustment for inter-study variability and inter-occasion assay variability in the simulation, IV golimumab 2 mg/kg + MTX at Weeks 0, 4 and q8w thereafter should yield similar steady-state trough concentrations as SC golimumab 50 mg q4w + MTX. The observed median trough serum golimumab concentrations in study CNTO148ART3001 were similar to simulated trough concentrations for 50 mg q4w SC in RA patients. Cmax's were however approximately six fold higher and exposures three fold higher for the proposed IV dosage as compared with 50 mg q4W SC dosing.

Figure 1 Simulated median serum golimumab concentration-time profiles following IV or SC administration of golimumab.



The effects of potential covariates on the PK parameters of golimumab were evaluated in the population analysis. The covariates examined included demographic characteristics, immune response, MTX use, baseline albumin, baseline CRP, baseline swollen joint count, baseline tender joint count,

Ex. 2052-009

diabetes comorbidity, smoking status, and white blood cell count. Among these covariates, weight, albumin, and age were statistically significant covariates ($p < 0.001$; chosen for multiplicity adjustment in covariate analysis). The number of subjects positive for antibodies to golimumab ($n = 40$) were so small that no conclusions regarding the effect of antibodies to golimumab on CL can be drawn.

In general, the effect of body weight on golimumab pharmacokinetics range from a decrease of 20% in exposure for patients with a body weight<50 kg to an increase of 50% for patients with a body weight ≥150 kg.

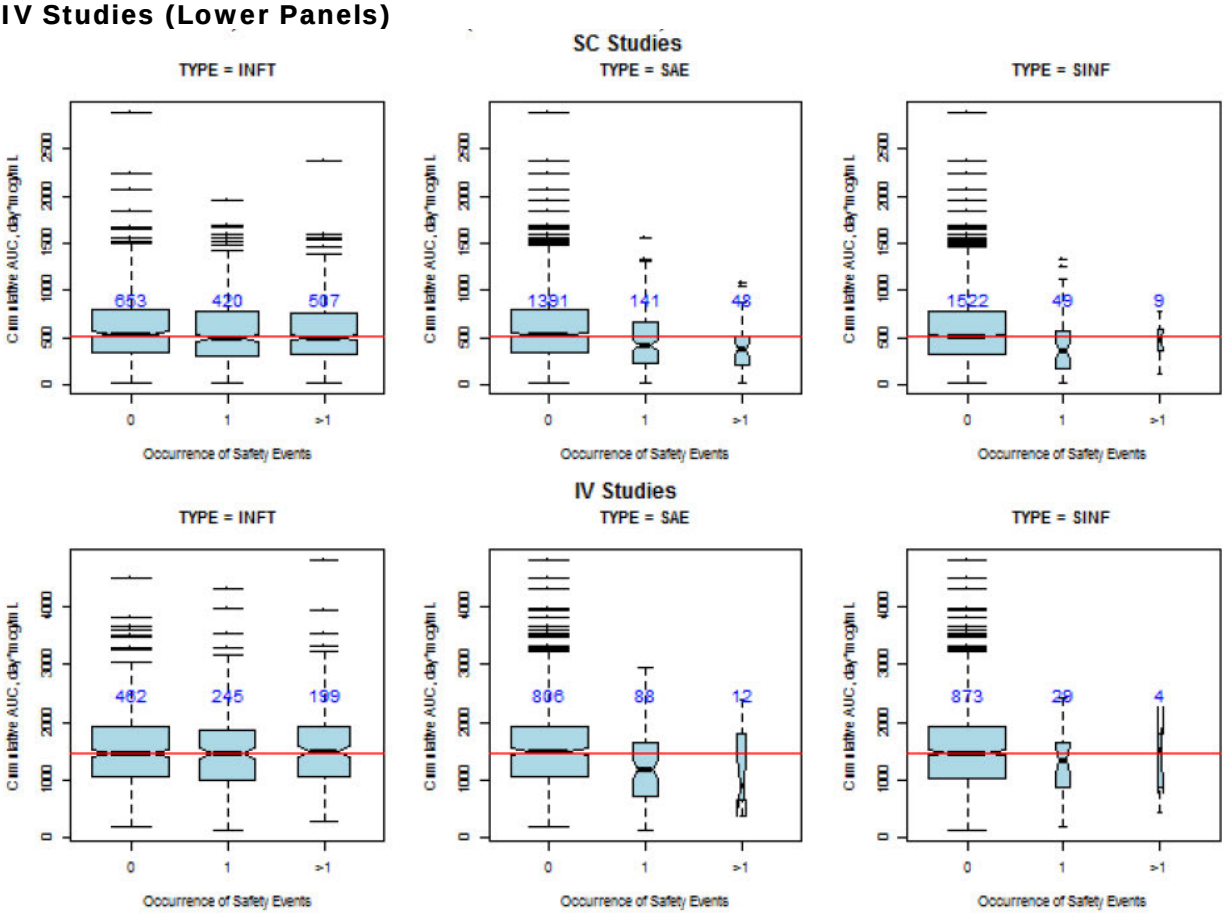
From quartile analysis of ACR response vs. serum golimumab concentration, a trend in increased ACR response at higher trough serum golimumab concentration was observed for both ACR 20 and ACR 50 response at Week 20, although trough serum golimumab concentrations above 0.40 µg/mL did not necessarily correlate with higher ACR response. Additionally, lower trough serum golimumab concentrations of 0.07 µg/ml to 0.21 µg/ml were effective, but did not lead to as high a proportion of subjects achieving ACR 20 or ACR 50 response compared with subjects with trough serum golimumab concentrations of 0.22 to 0.40 µg/mL and above.

The relation between golimumab exposure and selected safety variables was explored. The selected safety events that were chosen for the PK exposure/safety analysis were:

- Infections
- Serious infections
- SAEs
- Malignancies

Ex. 2052-010

Figure 2 Distribution of AUC (day*µg/mL) in Subjects with Increasing Occurrences of Selected Safety Events Through Week 52/Week48 in SC Studies (Upper Panels) and IV Studies (Lower Panels)



There was no clear trend of higher exposure in subjects who experienced 1 or more safety events, neither for IV nor for SC data. Since the occurrence (IV and SC combined) of serious infections and malignancies is rather low, 0.5% and 2%, respectively, firm conclusions regarding the distribution of exposure cannot be drawn.

Conclusions on clinical pharmacology

The pharmacokinetics of IV golimumab has been characterized in healthy volunteers as well as patients. Cmax was approximately 6-fold higher and exposures 3-fold higher for the proposed IV dosage as compared with 50 mg q4W SC dosing. Trough concentration was similar. A trend in increased ACR response at higher trough serum golimumab concentration was observed. There was no clear trend of higher exposure in subjects who experienced 1 or more safety events, neither for IV nor for SC data. However, a firm conclusion cannot be drawn due to the low number of adverse events.

Clinical efficacy

Dose-response studies and main clinical studies

The results from C0524T12 were used to develop the dosage regimen evaluated in the CNTO148ART3001 study, which is submitted as pivotal study for efficacy.

C0524T12 was a Phase 3 randomized, double-blind, placebo-controlled, multicenter, 5-arm study of the efficacy and safety of IV infusions of golimumab 2 mg/kg and 4 mg/kg (given with or without MTX)

Ex. 2052-011

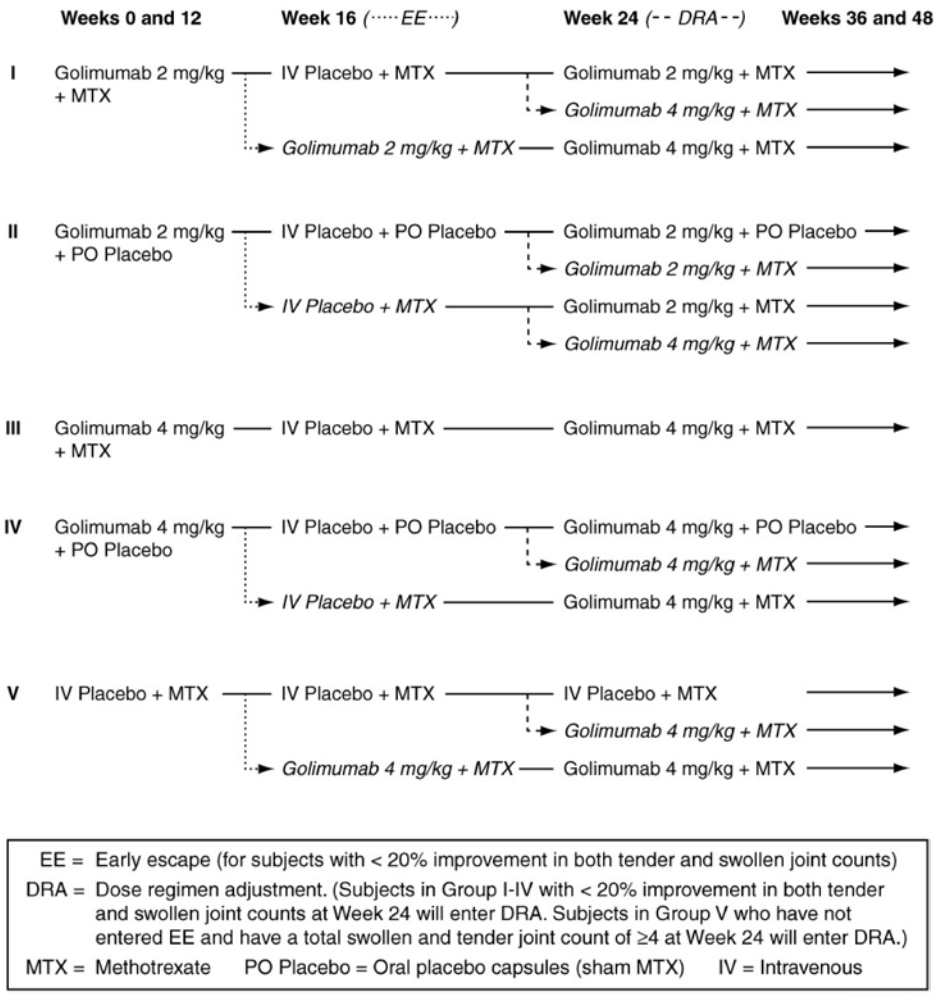
administered over a period of 30 minutes q12w for at least 48 weeks in subjects with moderately to severely active RA despite concurrent MTX therapy. At Week 16 and Week 24, joint assessment results were used to allow subjects to enter early escape and dose regimen adjustment, respectively, in a blinded fashion. All subjects were eligible for early escape at Week 16 if they demonstrated a < 20% improvement from baseline in both swollen and tender joint count. The subjects who did not meet the criteria for early escape at Week 16 and/or were not eligible for dose regimen adjustment at Week 24 received their randomized treatment through Week 48.

In addition to the above studies, the dossier contains study P06129, an open-label, multinational, multicenter, prospective study assessing the addition of SC golimumab to conventional disease-modifying antirheumatic drug (DMARD) therapy in biologic-naïve subjects with RA (Part 1), followed by a randomized study assessing the value of combined IV and SC golimumab administration versus SC administration aimed at inducing and maintaining DAS 28-ESR remission (Part 2).

The purpose of including study P06129 in this submission is to provide data on subjects using a combined IV/SC strategy in patients who were not in DAS 28-ESR remission with SC golimumab alone. The efficacy or safety data from study P06129 are not intended to contribute to the primary data presentation for this submission.

In this submission, baseline disease characteristics, demographics and efficacy results from the IV study CNTO148ART3001 are compared with those from the SC golimumab study C0524T06 to further support the overall comparability of efficacy of golimumab regardless of the route of administration.

Figure 3: Study Schema from Week 0 through Week 48 for C0524T12



Ex. 2052-012

Subjects who completed the final golimumab IV infusion before or within 3 months after the 48-week database lock were eligible to participate in the long-term extension phase of the study;those subjects who participated were switched from golimumab IV to golimumab 50 mg SC injections q4w, regardless of the dose of the IV infusions they received. Subjects who received IV placebo + MTX and had a total swollen and tender joint count of ≤ 3 were to discontinue study treatment. The first SC injection was to be administered 12 weeks after each subject completed his or her final IV infusion (ie, Week E-0).

The primary endpoint was the ACR 50 response at Week 14. ACR 50 response at Week 24 and ACR 20 response at Week 14 were major secondary endpoints. In addition, the proportions of subjects who achieved ACR 20, ACR 50, or ACR 70 responses were compared across treatment groups at selected timepoints (ie, at Week 14 or Week 24) and summarized over time through Week 24. DAS28 (using CRP) response at Week 14 was a major secondary endpoint.

The primary endpoint of ACR 50 response at Week 14 was not achieved. At Week 24, greater proportions of subjects in the individual and combined golimumab + MTX groups were ACR 20 and ACR 50 responders compared with the placebo + MTX group. For the golimumab 4 mg/kg + MTX group, the proportion of subjects with an ACR 50 response increased between Week 14 and Week 24, whereas the other treatment groups decreased. No notable differences were observed among treatment groups in the proportions of subjects who achieved an ACR 70 response at either Week 14 or Week 24 (Table 1).

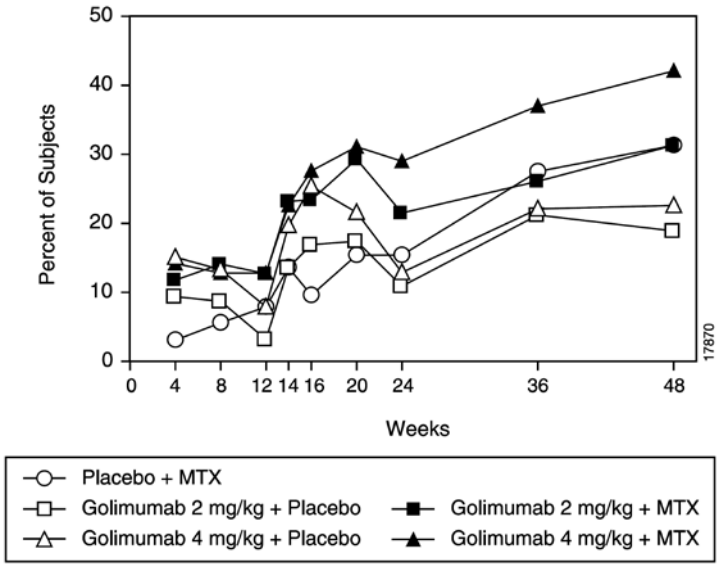
Table 1: Numbers of subjects who achieved ACR 20, 50, and 70 responses at Week 14 and Week 24; randomized subjects in C0524T12

		Golimumab					
		Golimumab Only			Golimumab + MTX		
	Placebo + MTX	2 mg/kg	4 mg/kg	Combined	2 mg/kg	4 mg/kg	Combined
Subjects randomized	129	128	129	257	129	128	257
ACR 20							
Week 14[a]	36 (27.9%)	51 (39.8%)	62 (48.1%)	113 (44.0%)	71 (55.0%)	66 (51.6%)	137 (53.3%)
Week 24	32 (24.8%)	29 (22.7%)	38 (29.5%)	67 (26.1%)	48 (37.2%)	64 (50.0%)	112 (43.6%)
ACR 50							
Week 14	**17 (13.2%)**	**16 (12.5%)**	**25 (19.4%)**	**41 (16.0%)**	**28 (21.7%)**	**27 (21.1%)**	**55 (21.4%)[b]**
Week 24[a]	12 (9.3%)	11 (8.6%)	15 (11.6%)	26 (10.1%)	24 (18.6%)	32 (25.0%)	56 (21.8%)
ACR 70							
Week 14	6 (4.7%)	5 (3.9%)	6 (4.7%)	11 (4.3%)	9 (7.0%)	7 (5.5%)	16 (6.2%)
Week 24	4 (3.1%)	4 (3.1%)	8 (6.2%)	12 (4.7%)	8 (6.2%)	10 (7.8%)	18 (7.0%)

Bold = Primary endpoint
[a] Major secondary endpoint
[b] p-value = 0.051

Ex. 2052-013

Figure 4: Proportion of subjects achieving ACR 50 response by visit through Week 48; randomized subjects in C0524T12



In C0524T12, neither the golimumab 2 mg/kg nor the 4 mg/kg q12w dosage regimens achieved the primary endpoint at Week 14. At Week 8, the median serum golimumab concentrations for the golimumab 2 mg/kg + MTX and the golimumab 4 mg/kg + MTX groups were 0.23 µg/mL and 0.53 µg /mL, respectively, whereas at Week 12, the median serum golimumab concentrations (ie, trough concentrations) were below the LLOQ (ie, < 0.2 µg/mL) for both treatment groups. The PK results in conjunction with the observed efficacy results suggested that the low systemic drug exposure in the later period of the 12-week dosage interval (ie, from Week 8 to Week 12) was the primary reason for the lack of a significant ACR response at Week 14. The following was therefore postulated for the design of the CNTO148ART3001 study:

- Based on the PK and efficacy findings from C0524T12, the dosage regimen was modified to use the lower dose previously studied in C0524T12 (ie, golimumab 2 mg/kg + MTX), but with an increased dosage frequency (ie, q8w).
- An additional dose of 2 mg/kg at Week 4 may lead to accentuation of ACR responses early in the process of managing inflammation and disease activity, which might then be maintained or increased with a q8w dosage regimen.
- Subjects should receive golimumab + MTX because of the low responses in the golimumab monotherapy groups in C0524T12.

Therefore, the dosage regimen chosen for CNTO148ART3001 was 2 initial doses of IV golimumab 2 mg/kg at Weeks 0 and 4, followed by a maintenance dosage regimen of IV golimumab 2 mg/kg q8w in combination with MTX. This is also the dose regimen applied for. Given the results as presented below, and with these arguments taken into account, it is considered that there is adequate support for the selected dose regimen applied for.

CNTO148ART3001 is a completed, Phase 3, randomized, double-blind, placebo-controlled, multicenter, 2-arm study of the efficacy and safety of IV infusions of golimumab 2 mg/kg administered over a period of 30 ± 10 minutes at Weeks 0, 4, and q8w through Week 100 in subjects with moderately to severely active RA despite concurrent MTX therapy. Subjects were randomized in a 2:1

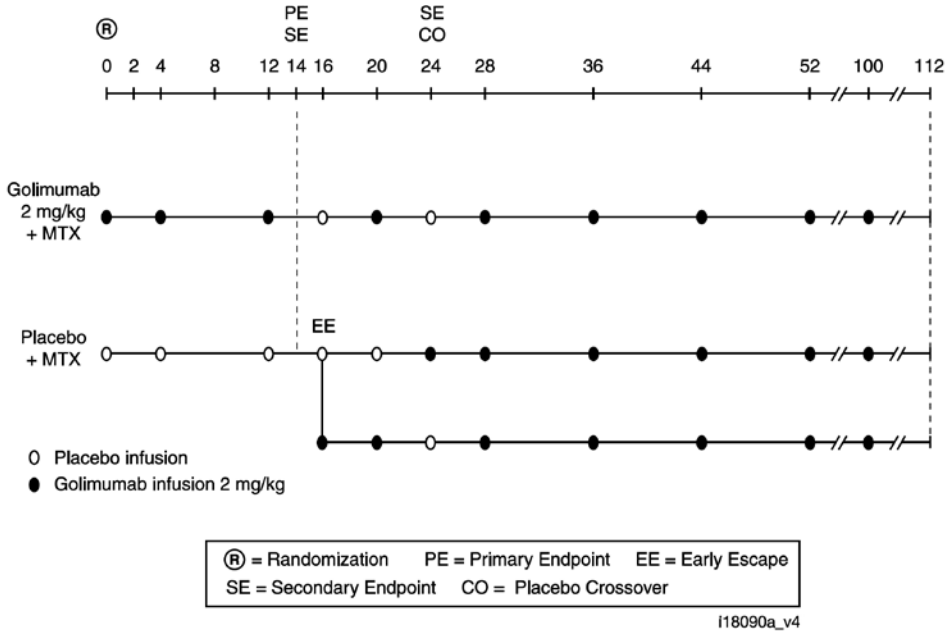
Ex. 2052-014

ratio to 1 of 2 treatment groups. Randomization was stratified by C-reactive protein (CRP) level at screening (< 1.5 mg/dL or ≥ 1.5 mg/dL) and investigational site.

Subjects initially randomized to placebo + MTX were eligible for early escape at Week 16 if they demonstrated a < 10% improvement in both swollen and tender joint count. Eligible subjects initiated golimumab 2 mg/kg infusions at Weeks 16, 20, and q8w thereafter. To maintain the blind, subjects (regardless of treatment group) with < 10% improvement in swollen and tender joints from baseline at Week 16 were required to obtain a radiograph of the hands and feet at Week 16. The criterion for early escape was set at < 10% improvement in both swollen and tender joint count in order to retain a larger number of subjects during the placebo-controlled period, compared to the previously used criterion of < 20% improvement in swollen and tender joint count in other studies of golimumab in subjects with moderately to severely active RA.

At Week 24, all remaining subjects in Group II who did not begin receiving golimumab 2 mg/kg infusions at Week 16 will start receiving golimumab 2 mg/kg at Weeks 24, 28, and subsequently every 8 weeks to Week 100.

Figure 5: Study Schema from Week 0 through Week 112 for CNTO148ART3001



Endpoints

The primary endpoint was the proportion of ACR 20 responders at Week 14.

The major secondary endpoints were:

1. The proportion of subjects with moderate or good DAS 28 response (using CRP) at Week 14.
2. Change from baseline in HAQ-DI at Week 14.
3. The proportion of subjects with ACR 50 response at Week 24.
4. Change from baseline in vdH-S score at Week 24 was planned for the Week 52 DBL and is not included in this CSR. This endpoint will be analyzed and reported in the Week 52 CSR.

Among other efficacy analyses were

1. Efficacy endpoints related to signs and symptoms of RA include ACR-related and DAS28 endpoints and their components.

Ex. 2052-015

2. ACR 20 at Week 24
3. ACR 50 at Week 14
4. ACR 70 at Week 14 and Week 24.

Various analyses of blood/serum were also undertaken both to address golimumab concentrations, antibodies, and selected inflammatory biomarkers.

Study population

In addition to age of at least 18 and RA diagnosis according the revised ARA criteria, main inclusion criteria were:

- Subjects must have been treated with and tolerated MTX at a dose of at least 15 mg/week for at least 3 months prior to screening, and have been on a stable MTX dose of ≥15 mg/week and ≤25 mg/week for at least 4 weeks prior to screening.
- Have active RA, as defined by persistent disease activity with at least 6 swollen and 6 tender joints, at the time of screening and at baseline.
- CRP ≥ 1.0 mg/dL at screening.
- Anti-cyclic citrullinated peptide (anti-CCP) antibody-positive or rheumatoid factor (RF)-positive at screening.
- If using NSAIDs or other analgesics for RA, must be on a stable dose for at least 2 weeks prior to the first administration of study agent.
- If using oral corticosteroids, must be on a stable dose equivalent to ≤ 10 mg of prednisone/day for at least 2 weeks prior to first administration of study agent.

Since the CRP inclusion criterion requested a value of ≥ 1.0mg/dL at screening, it could be lower by the time of baseline visit, up to 6 weeks later. This was the case for 63 subjects (32%) in the PBO group, and 99 subjects (25%) in the golimumab-treated group. If the purpose was to include only subjects with a certain disease activity it would have been more appropriate to relate this inclusion criterion to the baseline visit.

Main exclusion criteria included:

- Other inflammatory diseases, including but not limited to PsA, AS, systemic lupus erythematosus, or Lyme disease, that might confound the evaluation of the benefit of golimumab therapy
- Treatmen with DMARDs (other than MTX)/systemic immunosuppressives during the 4 weeks prior to first administration of study agent.
- Administration of intra-articular, IM, or IV corticosteroids, including adrenocorticotropic hormone, during the 4 weeks prior to first administration of study agent.
- Have received TNF-blockers or cytotoxic agents or agents that target alpha-4 integrin.

Statistical analyses

For the primary analyses, if a subject discontinued because of treatment failure, that subject was treated as a non-responder in the analysis. If a subject discontinued for other reasons, the data was treated as missing and the last observation carried forward was used in the data analysis.

The LOCF approach for some of the discontinuing patients is not necessarily conservative, depending on the actual withdrawal pattern. See further below.

Ex. 2052-016

If a subject met the early escape criteria at Week 16, each endpoint or component value after Week 16 was replaced with the corresponding component value at Week 16.

Summary of main efficacy results

Table 2: Number of subjects through Week 24 by study treatment assigned vs study treatment received; randomized subject

	Placebo + MTX	Golimumab 2 mg/kg + MTX
Subjects randomized	197	395
Subjects treated	197	395
Treatment received[a]		
Placebo + MTX	129 (65.5%)	0 (0.0%)
Placebo + MTX → golimumab 2 mg/kg + MTX	68 (34.5%)	0 (0.0%)
Golimumab 2 mg/kg + MTX	0 (0.0%)	395 (100.0%)

[a] Subjects who early escaped at Week 16 started receiving golimumab at Week 16.

Table 3: Number of subjects who discontinued study agent through Week 24; randomized subjects

	Placebo + MTX	Golimumab 2 mg/kg + MTX	Total
Subjects randomized	197	395	592
Subjects ongoing and continuing study agent	191 (97.0%)	379 (95.9%)	570 (96.3%)
Subjects ongoing and discontinued study agent	3 (1.5%)	5 (1.3%)	8 (1.4%)
Subjects who discontinued study agent and completed post-treatment follow-up	1 (0.5%)	7 (1.8%)	8 (1.4%)
Subjects who discontinued study agent and did not complete post-treatment follow-up	2 (1.0%)	4 (1.0%)	6 (1.0%)
Reason for discontinuing study agent[a]			
Death	1 (0.5%)	0 (0.0%)	1 (0.2%)
Lost to follow-up	0 (0.0%)	1 (0.3%)	1 (0.2%)
Withdrawal of consent	2 (1.0%)	4 (1.0%)	6 (1.0%)
Adverse event	2 (1.0%)	9 (2.3%)	11 (1.9%)
Lack of efficacy	1 (0.5%)	1 (0.3%)	2 (0.3%)
Protocol violation	0 (0.0%)	1 (0.3%)	1 (0.2%)

[a] Percentages calculated with the number of subjects in each group as denominator.

By week 24, 35% of placebo + MTX treated subjects had switched to active treatment. However, few subjects discontinued treatment during the 24 weeks period. There was a slightly higher number in the golimumab treated group who discontinued (4.1% vs 3% for placebo), and this was due to subjects discontinuing due to adverse events (2.3% vs 1 % for placebo). These data do not raise specific concern or compromise the evaluation of efficacy.

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Table 4: Summary of baseline disease characteristics of RA for ACR core set of measurements; randomized subjects

	Placebo + MTX	Golimumab 2 mg/kg + MTX	Total
Subjects randomized	197	395	592
Number of swollen joints (0-66)			
n	197	395	592
Mean ± SD	14.8 ± 8.54	15.0 ± 8.23	14.9 ± 8.33
Median	12.0	12.0	12.0
IQ range	(8.0, 19.0)	(9.0, 19.0)	(9.0, 19.0)
Range	(5, 47)	(4, 56)	(4, 56)
Number of tender joints (0-68)			
n	197	395	592
Mean ± SD	25.9 ± 14.13	26.4 ± 13.93	26.3 ± 13.99
Median	22.0	24.0	23.0
IQ range	(14.0, 36.0)	(15.0, 35.0)	(15.0, 35.0)
Range	(6, 68)	(5, 68)	(5, 68)
CRP (mg/dL)			
n	197	395	592
Mean ± SD	2.234 ± 1.8793	2.847 ± 2.8570	2.643 ± 2.5878
Median	1.720	2.020	1.935
IQ range	(0.899, 3.020)	(0.998, 3.430)	(0.943, 3.285)
Range	(0.02, 10.60)	(0.07, 21.10)	(0.02, 21.10)
Physician's global assessment of disease (VAS; 0-10 cm)			
n	197	395	592
Mean ± SD	6.27 ± 1.580	6.22 ± 1.652	6.24 ± 1.627
Median	6.30	6.30	6.30
IQ range	(5.40, 7.40)	(5.10, 7.40)	(5.20, 7.40)
Range	(0.2, 9.5)	(1.5, 10.0)	(0.2, 10.0)
Patient's global assessment of disease (VAS; 0-10 cm)			
n	197	395	592
Mean ± SD	6.50 ± 1.947	6.45 ± 1.834	6.47 ± 1.871
Median	6.90	6.60	6.70
IQ range	(5.10, 7.90)	(5.10, 7.80)	(5.10, 7.90)
Range	(0.7, 10.0)	(1.4, 10.0)	(0.7, 10.0)

Baseline values for the non-ACR core set of measurements indicated moderate to severe RA, and were similar between the treatment groups. The median baseline DAS28 score was 5.9 indicative of severe disease. In addition, 92.8% of subjects in the placebo + MTX dose group and 91.9% of subjects in the golimumab + MTX dose group were positive for anti-CCP antibodies. In addition, 91.9% of subjects in the placebo + MTX dose group and 92.4% of subjects in the golimumab + MTX dose group were RF positive at baseline. The high number of tender and swollen joints and the high DAS 28 score in combination with request of either positive RF or CCP antibodies, predictors of joint destruction, indicate that the studied population had a highly active disease and high risk of future structural damage.

A medication or therapy was considered concomitant at baseline if it had been used both prior to and after the first study agent administration. The proportions of subjects at baseline taking oral corticosteroids (64-68%) or NSAIDs (79-82%) specifically for RA were generally similar across both treatment groups

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Primary endpoint, result

Table 5: Number of subjects who achieved an ACR 20 response at Week 14; randomized subjects		
	Placebo + MTX	Golimumab 2 mg/kg + MTX
Subjects randomized	197	395
ACR 20 n	197	395
Subjects in response	49 (24.9%)	231 (58.5%)
p-value	< 0.001	

The difference in response rate between groups is 33.6%. This result is clinically relevant.

Table 6: Number of subjects who achieved an ACR 20 response at Week 14 by screening CRP level; randomized subjects

	Placebo + MTX	Golimumab 2 mg/kg + MTX
Subjects randomized	197	395
Subjects with screening CRP < 1.5 mg/dL	34	69
ACR 20		
n	34	69
Subjects in response	8 (23.5%)	42 (60.9%)
p-value		< 0.001
Subjects with screening CRP ≥ 1.5 mg/dL	163	326
ACR 20		
n	163	326
Subjects in response	41 (25.2%)	189 (58.0%)
p-value		< 0.001

Since inclusion criteria requested a CRP not less than 1.0mg/dL at screening, the population with less than 1.5mg/dL at screening reasonably had values in the interval 1.0-1.4mg/dL. The comparison thus adds little information. However, another analysis, addressing subjects with >1.0mg/dL and <1.0mg/dL at baseline has also been performed and is presented below.

Since the primary efficacy analysis was statistically significant, tests were performed for the major secondary endpoints in the following sequential order correcting for multiplicity.

Secondary endpoints, results

Proportion of Subjects With DAS28 Response (Using CRP at Week 14)

Table 7: Number of DAS28 (using CRP) responders with moderate or good response at Week 14; randomized subjects

	Placebo + MTX	Golimumab 2 mg/kg + MTX
Subjects randomized	197	395
Week 14		
n	197	395
Subjects with moderate or good response	79 (40.1%)	321 (81.3%)
p-value		< 0.001

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The results show that a robust DAS28 response was achieved receiving golimumab 2 mg/kg + MTX regardless of screening CRP level. In subjects with a screening CRP level < 1.5 mg/dL, there was a greater response in the golimumab + MTX treatment group relative to the placebo + MTX group (82.6% compared with 44.1%, respectively). In subjects with a screening CRP level ≥ 1.5 mg/dL, there was a greater response in the golimumab + MTX treatment group with the placebo + MTX group (81.0% versus 39.3%, respectively).

Change in Baseline From HAQ-DI at Week 14

At Week 14, improvement in HAQ-DI score from baseline at Week 14 was significantly greater in the golimumab + MTX group than in the placebo + MTX group (median 0.5000 compared with 0.1250, respectively, p < 0.001). Mean improvement in HAQ-DI at Week 14 was 0.4962 ± 0.5771 in the golimumab + MTX group and 0.1902 ± 0.5577 in the placebo + MTX group.

Subjects treated with golimumab + MTX, who had a screening CRP level < 1.5 mg/dL had a similar difference between golimumab and placebo in HAQ-DI improvement from baseline relative to subjects who had a screening CRP level ≥ 1.5 mg/dL:

ACR 50 Response at Week 24

Table 8: Number of subjects who achieved an ACR 50 response at Week 24; randomized subjects

	Placebo + MTX	Golimumab 2 mg/kg + MTX
Subjects randomized	197	395
ACR 50		
n	197	395
Subjects in response	26 (13.2%)	138 (34.9%)
p-value		< 0.001

ACR 50 response at Week 24 by screening CRP level shows that a robust ACR 50 response is achieved regardless of CRP level:

5. 39.1% of subjects who had a screening CRP level < 1.5 mg/dL and were treated with golimumab + MTX had an ACR 50 response compared with 14.7% of subjects treated with placebo + MTX.
6. 34.0% of subjects who had a screening CRP level ≥ 1.5 mg/dL and were treated with golimumab + MTX had an ACR 50 response compared with 12.9% of subjects treated with placebo + MTX.

Change in Baseline in van der Heijde Modified Sharp Score at Week 24

The probability plot for the change from baseline in vdH-S score at Week 24 is shown in Figure 6.

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Figure 6: Probability plot for change from baseline in total van der Heijde modified Sharp score at Week 24; randomized subjects

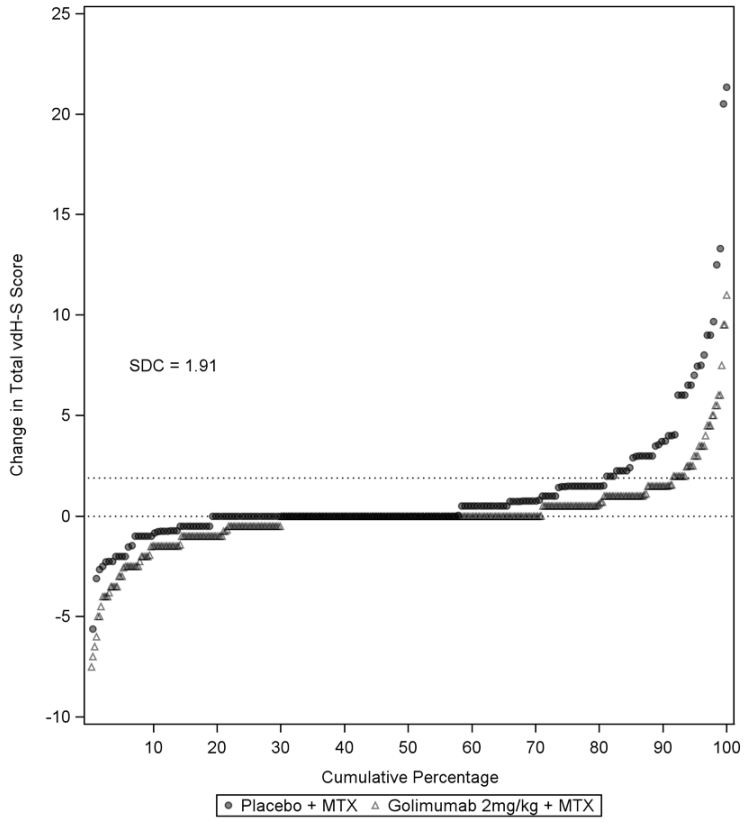

Table 9 provides an overview of the radiographic analyses at Week 24, Week 52, and Week 100, respectively.

Table 9: Summary of radiographic analyses at Week 100; randomized subjects in CNTO148ART3001*

	Placebo + MTX → golimumab + MTX[a]	Golimumab 2 mg/kg + MTX
Subjects randomized	197	395
Change from baseline in total vdH-S score at Week 100		
Mean (SD)	2.10 (7.417)	0.74 (6.318)
p-value		0.005
Change from baseline in erosion score at Week 100		
Mean (SD)	0.43 (4.623)	-0.07 (3.679)
Change from baseline in JSN score at Week 100		
Mean (SD)	1.67 (3.907)	0.81 (3.562)

a Includes subjects randomized to placebo + MTX at Week 0 who began receiving golimumab + MTX at Week 16 due to early escape or at Week 24 due to crossover from placebo

Change in Baseline in van der Heijde Modified Sharp Score at Week 24 has been analyzed and shows a positive effect on structural damage, since the change from baseline in vdH-S score at Week 24 was significantly greater in the subjects receiving placebo +MTX than in the subjects receiving IV golimumab + MTX.

<u>Subgroup Analysis Based on Week 0 CRP</u>

To be included in the study, a subject's CRP level at screening had to be ≥ 1.0 mg/dL. However, by Week 0 (up to 6 weeks after the screening visit), it was observed that the CRP levels for some subjects had decreased below the 1.0 mg/dL level. To differentiate these subjects, analyses for selected endpoints were also analyzed by Week 0 CRP levels (< 1.0 mg/dL and ≥ 1.0 mg/dL). There were 63

Ex. 2052-021

(32.0%) subjects in the placebo + MTX group and 99 (25.1%) of subjects in the golimumab + MTX group who had Week 0 CRP levels < 1.0 mg/dL.

58.6% of subjects who had a Week 0 CRP level < 1.0 mg/dL and 58.8% of subjects who had a Week 0 CRP level ≥ 1.0 mg/dL and were treated with golimumab + MTX had an ACR 20 response relative to 30.2% and 22.4%respectively of subjects treated with placebo + MTX.

ACR responses after Week 24 through Week 52 and Week 100

Table 10: Numbers of subjects who achieved ACR 20, 50, and 70 responses at Week 52 randomized subjects in study CNTO148ART3001

	Placebo + MTX	Golimumab 2 mg/kg + MTX
Subjects randomized	197	395
Week 52		
Subjects with ACR 20 response	121 (61.4%)	260 (65.8%)
Subjects with ACR 50 response	62 (31.5%)	153 (38.7%)
Subjects with ACR 70 response	29 (14.7%)	72 (18.2%)

Abbreviations: ACR = American College of Rheumatology; MTX = methotrexate

The proportions of subjects in the golimumab + MTX group who achieved ACR 20, ACR 50, and ACR 70 responses were generally maintained or increased after Week 24 through Week 52 and generally maintained or increased after Week 52 through week 100. Subjects in the placebo + MTX → golimumab + MTX group, which included subjects who were eligible for early escape at Week 16 or who crossed over to golimumab at Week 24, also started responding after switching to golimumab treatment by Week 28 and generally maintained through Week 52 and generally maintained responses after Week 52 through Week 100 at a rate similar to subjects initially randomized to golimumab + MTX through week 100 at a rate similar to subjects initially randomized to golimumab+MTX.

A clinically relevant percent (for ACR 20: 37.9-47.4%; for ACR 50: 23.3-30.3%; for ACR 70: 13.3-16.0%) of subjects who were not responders at either Week 52 or Week 24 became responders for the individual measurements by Week 100.

Table 11: Numbers of subjects who achieved ACR 20, 50, and 70 responses at Week 100; randomized subjects in study CNTO148ART3001

	Placebo + MTX	Golimumab 2 mg/kg + MTX
Subjects randomized	197	395
Week 100		
Subjects with ACR 20 response	130 (66.0%)	273 (69.1%)
Subjects with ACR 50 response	81 (41.1%)	178 (45.1%)
Subjects with ACR 70 response	47 (23.9%)	92 (23.3%)

Supportive study P06129

This was an open-label, multinational, multicenter, prospective study assessing the addition of SC golimumab to conventional disease-modifying antirheumatic drug (DMARD) therapy in biologic-naïve subjects with RA (Part 1), followed by a randomized study assessing the value of combined IV and SC golimumab administration versus SC administration aimed at inducing and maintaining DAS 28-ESR remission (Part 2). Approximately 3357 subjects were randomized in Part 1, and approximately 505 subjects randomized to Part 2.

Results

In Part I of the study, at Week 24, the percentage of subjects achieving DAS28 (ESR) response was 82.1%. In Part 2 of the study, the percentage of subjects with DAS28 (ESR) remission at the start of

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Month 11 was 24.0% and 25.8% of subjects in the IV golimumab 2 mg/kg → SC golimumab 50 mg and SC golimumab 50 mg treatment groups, respectively, and at the end of Month 12 was 24.4% and 27.0% of subjects, respectively. No significant difference between treatment groups was observed for the proportion of subjects with DAS28 (ESR) remission at the start of Month 11 or end of Month 12 thus indicating maintenance of effect with golimumab regardless of route of administration.

This study did not show any advantage in using IV administration to achieve remission in patients with partial response to golimumab. However, the interest in this study lies in the safety profile for switching between formulations. This aspect is discussed in the safety section.

Discussion on clinical efficacy

The applicant has currently market authorization for Simponi 50mg/ml prefilled syringes for sc injections every fourth week. The indications are

- the treatment of moderate to severe, active rheumatoid arthritis in adults when the response to disease-modifying anti-rheumatic drug (DMARD) therapy including MTX has been inadequate
- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX
- Psoriatic Arthritis
- Ankylosing Spondylitis

The MAH is now applying for authorization to market a formulation for intravenous administration. The indication applied for is second line treatment of RA.

The reason for adding IV Simponi to the therapeutic arsenal is according to the MAH that *"IV golimumab, with its less frequent dosing necessitating fewer office visits, provides an important treatment option to those patients who have difficulty performing self-injection and cannot get help from family members, healthcare professionals or other caregivers to administer the SC treatment at home."*

With the current application, safety and efficacy data from study CNTO148ART3001 has been provided, and the MAH has performed inter study comparisons between a SC study, C0524T06, investigating RA patients with inadequate response to MTX, and study CNTO148ART3001. Also, a document addressing patient categories that may benefit from IV Simponi has been submitted.

In addition, study P06129 has been included in order to provide data for switching SC to IV/SC administration.

The first phase 3 study with IV golimumab, CO524T12, did not meet the primary endpoint, ACR 50% at Week 14. This was due to the 12 weeks long dosing interval, resulting in undetectable serum concentration of golimumab during the latter part of the dosing interval. The experience from this study was used when designing study CNTO148ART3001. In this study golimumab was dosed 2mg/kg Week 0, 4 and 8 and thereafter every 8th week, which is the posology applied for. The dose selection and dose applied for are acceptable given the totality of data submitted.

Study CNTO148ART3001 has shown efficacy of IV Simponi over placebo. There was a difference of 33.6% between the active treatment group and the placebo group in the primary endpoint, ACR 20% at week 14, which compares well with the effects demonstrated for the SC formulation compared with placebo. The results seem robust; the subjects were stratified for CRP-levels, and the figures are similar in both subgroups. Also ACR 50 at week 14, which was the unmet primary endpoint in study CO524T12 showed a statistically significant difference (21.3%, $p < 0.001$) between the groups. The 4 secondary endpoints, DAS 28 response at Week 14 (41.2%), improvement in HAQ-DI score from

Ex. 2052-023

baseline (0.3750) ACR 50 response at Week 24 (21.7%) and change from baseline in vdH-S score at Week 24 were also met.

Efficacy data from Weeks 52 and 112 from study CNTO148ART3001 show that the clinical benefits appear to be maintained over time. However, development of antibodies appears to reduce the response rate.

It was pointed out that a trial design with sc Simponi as comparator would have provided significantly more information. Important items that could have been compared are time to onset of effect, effect size, AE frequency, and incidence of certain AE, such as infections. Also issues regarding switching between the formulations could have been enlightened. In order to fill in this information gap, the MAH has presented an inter study comparison, across the 2 IV studies, CNTO148ART3001 and CO524T12 and one of the SC studies from the SC dossier, C0524T06. This study was chosen as it also enrolled a MTX inadequate-responder subject population similar to that in CNTO148ART3001. The choice is endorsed. It is however important to bear in mind that the populations differ in terms of disease activity. CNTO148ART3001 required at least 6 swollen and at least 6 tender joints at screening and baseline, a mandatory CRP ≥ 1.0 mg/dL at screening, and rheumatoid factor (RF) positivity and/or anti-cyclic citrullinated peptide (anti-CCP) positivity at screening, whereas, in studies and C0524T06 (or in C0524T12), elevated CRP (≥ 1.0 mg/dL) was not required and only 4 swollen and 4 tender joints were required for inclusion.

However, it is acknowledged that golimumab IV 2mg/kg Q8W appears to be similar to SC administration in terms of efficacy. Safety comparisons are discussed further down in this document.

It is noted that there is a trend towards higher risk of developing antibodies after 24 weeks on IV treatment (no case in the SC T06 study although it should be noted that this cohort was smaller). This tendency remains at Weeks 52 and 100, where the overall antibody to golimumab incidences for CNTO148ART3001 were 4.6% and 6.7% respectively. At week 52 in the T06 study, 1.1% in the combined SC golimumab + MTX group had developed antibodies to golimumab. Also, a trend towards a weakened response in antibody positive patients at Week 100 is shown, with 51.4% ACR20 response and 29.7% ACR 50 response for antibody positive subjects, as compared to 70.3% and 45.9% respectively for antibody negative subjects.

In order to address the concern regarding which patients may benefit from IV administration, the MAH presented data from 3 SC clinical trials (C0524T05. C0524T06 and C0524T11), an open observational study on patients in Northern America and 2 patient surveys. Approximately 30% of subjects in these RA studies with SC formulation preferred not to self inject. The reason for this was not collected. When reviewing characteristics of this patient group, they had a slightly higher HAQ-DI score at baseline, but not significantly higher disease activity as measured by DAS 28. They were slightly older. It is also noted that there was a significant difference between regions, indicating that tradition and/or expectations from the caregiver may play a role. The retrospective observational study did not contradict the above results. The patients surveys showed that around 25% of patients on SC administration did not self inject. The reason for IV preference was investigated, however in a population where only half of the subjects had RA, and by asking the subjects to compare IV administration to SC administration every or every two weeks instead of Q4W, making it difficult to draw conclusions. It is noted that inconvenience with logistic issues and uncomfortable/painful shots totals around 10% of the patients.

Taken together, it is acknowledged that there are patients who are not able to inject themselves and therefore need help to use the SC formulation. Some of these would need to come to a health care office every four weeks. However, the additional benefit of less frequent visits still is weak.

Ex. 2052-024

Conclusions on clinical efficacy

The results from study CNTO148ART3001 convincingly show that the proposed dosing of IV golimumab is effective, although the lack of direct comparison to SC administration was considered a shortcoming. The submitted inter study comparisons also supports the efficacy of IV administration. The submitted summary on patients that may benefit from IV administration only partly addresses the targeted population, and has not convincingly pointed out a patient group for which IV administration would be preferable from a medical perspective. There may be a small group of patients for which SC administration is no option due to pain or fear, but this has not been shown in the targeted population.

Clinical safety

The safety of golimumab was assessed in depth in the original application in 2009, and subsequently PSURs have been assessed. The focus of the current report will therefore be on the new safety data from use of golimumab given i.v., and to assess whether the safety profile of i.v. use is in line with that of s.c. administration.

For targeted safety events, data from the Phase 3 RA IV studies were integrated with selected data from the previously assessed Phase 2b RA subcutaneous (SC) and Phase 3 RA, psoriatic arthritis [PsA], and ankylosing spondylitis [AS] SC studies, the Phase 2b asthma SC study, and the Phase 1 RA IV and SC and uveitis SC studies.

CNTO148ART3001 is a completed study, where the last Week 24 visit occurred on 18 May 2011. For the CNTO148ART3001 study, safety data through 15 August 2012 (after all subjects completed at least 52 weeks) are included and incorporated in integrated analyses. In addition, safety data from CNTO148ART3001 through Week 112 (study completion) are also presented. C0524T12 was completed in 2010. Even though the study did not meet its primary efficacy endpoint, the safety data are useful for assessing the safety profile of the intravenous formulation.

Data on subjects who switched from IV to SC formulation are available as part of study C0524T12. The safety of using an IV/SC strategy in patients who were not in remission with golimumab SC was evaluated in Part 2 of study P06129.

Patient exposure

Through 15 August 2012 in the integrated Phase 3 RA IV studies, 1210 subjects received at least 1 dose of golimumab, 209 subjects received golimumab for >24 to <52 weeks, and 975 subjects received golimumab for more than 52 weeks. The median number of golimumab administrations was 7.0 and the median cumulative dose was 1450.0 mg. The median duration of follow-up was 72.7 weeks.

Overall, this amount of exposure is sufficient to support the safety assessment of the i.v. formulation. The relatively short pure placebo-controlled period limits the interpretations somewhat, but is in accordance with how previous studies have been designed in the second line population.

Ex. 2052-025

Adverse events

Table 12: Number of subjects with any AEs (frequency of >= 1% and < 5% in the golimumab group in all studies) through Week 16 by MedDRA SOC and PT; treated subjects in RA Phase 3 intravenous studies

	C0524T12			ART3001		All Studies	
		Golimumab					
	Placebo	2 mg/kg q12	4 mg/kg q12	Placebo	Golimumab 2 mg/kg q8[a]	Placebo	Golimumab
Treated subjects in RA Phase 3 intravenous studies	129	258	255	197	395	326	908
Avg duration of follow-up (weeks)	15.9	16.0	16.0	15.9	15.9	15.9	15.9
Avg exposure (number of administrations)	2.0	2.0	2.0	2.9	2.9	2.6	2.4
Subjects with any adverse events	87 (67.4%)	170 (65.9%)	168 (65.9%)	86 (43.7%)	187 (47.3%)	173 (53.1%)	525 (57.8%)
System-organ class/preferred term							
Infections and infestations	42 (32.6%)	77 (29.8%)	89 (34.9%)	41 (20.8%)	96 (24.3%)	83 (25.5%)	262 (28.9%)
Nasopharyngitis	3 (2.3%)	10 (3.9%)	11 (4.3%)	4 (2.0%)	8 (2.0%)	7 (2.1%)	29 (3.2%)
Urinary tract infection	2 (1.6%)	4 (1.6%)	12 (4.7%)	5 (2.5%)	10 (2.5%)	7 (2.1%)	26 (2.9%)
Sinusitis	4 (3.1%)	7 (2.7%)	11 (4.3%)	3 (1.5%)	6 (1.5%)	7 (2.1%)	24 (2.6%)
Pharyngitis	3 (2.3%)	3 (1.2%)	12 (4.7%)	1 (0.5%)	8 (2.0%)	4 (1.2%)	23 (2.5%)
Bronchitis	5 (3.9%)	7 (2.7%)	6 (2.4%)	0 (0.0%)	5 (1.3%)	5 (1.5%)	18 (2.0%)
Influenza	1 (0.8%)	7 (2.7%)	2 (0.8%)	4 (2.0%)	3 (0.8%)	5 (1.5%)	12 (1.3%)
Gastroenteritis	2 (1.6%)	2 (0.8%)	4 (1.6%)	1 (0.5%)	5 (1.3%)	3 (0.9%)	11 (1.2%)
Viral infection	1 (0.8%)	4 (1.6%)	3 (1.2%)	1 (0.5%)	3 (0.8%)	2 (0.6%)	10 (1.1%)
Rhinitis	4 (3.1%)	4 (1.6%)	3 (1.2%)	0 (0.0%)	2 (0.5%)	4 (1.2%)	9 (1.0%)
	C0524T12			ART3001		All Studies	
		Golimumab					
	Placebo	2 mg/kg q12	4 mg/kg q12	Placebo	Golimumab 2 mg/kg q8[a]	Placebo	Golimumab
Gastrointestinal disorders	28 (21.7%)	45 (17.4%)	41 (16.1%)	11 (5.6%)	26 (6.6%)	39 (12.0%)	112 (12.3%)
Nausea	7 (5.4%)	11 (4.3%)	17 (6.7%)	1 (0.5%)	4 (1.0%)	8 (2.5%)	32 (3.5%)
Diarrhoea	2 (1.6%)	8 (3.1%)	8 (3.1%)	2 (1.0%)	6 (1.5%)	4 (1.2%)	22 (2.4%)
Dyspepsia	2 (1.6%)	9 (3.5%)	7 (2.7%)	2 (1.0%)	3 (0.8%)	4 (1.2%)	19 (2.1%)
Vomiting	5 (3.9%)	6 (2.3%)	7 (2.7%)	1 (0.5%)	1 (0.3%)	6 (1.8%)	14 (1.5%)
Abdominal pain upper	0 (0.0%)	7 (2.7%)	3 (1.2%)	0 (0.0%)	2 (0.5%)	0 (0.0%)	12 (1.3%)
Musculoskeletal and connective tissue disorders	17 (13.2%)	33 (12.8%)	40 (15.7%)	29 (14.7%)	27 (6.8%)	46 (14.1%)	100 (11.0%)
Rheumatoid arthritis	4 (3.1%)	12 (4.7%)	10 (3.9%)	11 (5.6%)	6 (1.5%)	15 (4.6%)	28 (3.1%)
Arthralgia	4 (3.1%)	6 (2.3%)	12 (4.7%)	7 (3.6%)	6 (1.5%)	11 (3.4%)	24 (2.6%)
Back pain	4 (3.1%)	8 (3.1%)	4 (1.6%)	4 (2.0%)	4 (1.0%)	8 (2.5%)	16 (1.8%)
Pain in extremity	0 (0.0%)	4 (1.6%)	3 (1.2%)	1 (0.5%)	2 (0.5%)	1 (0.3%)	9 (1.0%)
Nervous system disorders	16 (12.4%)	24 (9.3%)	37 (14.5%)	8 (4.1%)	27 (6.8%)	24 (7.4%)	88 (9.7%)
Dizziness	2 (1.6%)	3 (1.2%)	5 (2.0%)	1 (0.5%)	1 (0.3%)	3 (0.9%)	9 (1.0%)
Skin and subcutaneous tissue disorders	9 (7.0%)	35 (13.6%)	18 (7.1%)	7 (3.6%)	26 (6.6%)	16 (4.9%)	79 (8.7%)
Rash	0 (0.0%)	9 (3.5%)	3 (1.2%)	1 (0.5%)	5 (1.3%)	1 (0.3%)	17 (1.9%)
Alopecia	1 (0.8%)	6 (2.3%)	4 (1.6%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	10 (1.1%)
Pruritus	0 (0.0%)	2 (0.8%)	1 (0.4%)	1 (0.5%)	6 (1.5%)	1 (0.3%)	9 (1.0%)
Respiratory, thoracic and mediastinal disorders	16 (12.4%)	17 (6.6%)	26 (10.2%)	5 (2.5%)	19 (4.8%)	21 (6.4%)	62 (6.8%)
Cough	4 (3.1%)	8 (3.1%)	10 (3.9%)	0 (0.0%)	4 (1.0%)	4 (1.2%)	22 (2.4%)
Investigations	15 (11.6%)	22 (8.5%)	21 (8.2%)	8 (4.1%)	15 (3.8%)	23 (7.1%)	58 (6.4%)
Alanine aminotransferase increased	7 (5.4%)	8 (3.1%)	7 (2.7%)	3 (1.5%)	4 (1.0%)	10 (3.1%)	19 (2.1%)

Ex. 2052-026

	C0524T12			ART3001		All Studies	
		Golimumab			Golimumab		
	Placebo	2 mg/kg q12	4 mg/kg q12	Placebo	2 mg/kg q8[a]	Placebo	Golimumab
Vascular disorders	5 (3.9%)	20 (7.8%)	10 (3.9%)	5 (2.5%)	15 (3.8%)	10 (3.1%)	45 (5.0%)
Hypertension	2 (1.6%)	11 (4.3%)	7 (2.7%)	3 (1.5%)	11 (2.8%)	5 (1.5%)	29 (3.2%)
General disorders and administration site conditions	11 (8.5%)	12 (4.7%)	16 (6.3%)	5 (2.5%)	11 (2.8%)	16 (4.9%)	39 (4.3%)
Pyrexia	0 (0.0%)	2 (0.8%)	1 (0.4%)	0 (0.0%)	8 (2.0%)	0 (0.0%)	11 (1.2%)
Injury, poisoning and procedural complications	9 (7.0%)	11 (4.3%)	15 (5.9%)	6 (3.0%)	7 (1.8%)	15 (4.6%)	33 (3.6%)
Psychiatric disorders	3 (2.3%)	8 (3.1%)	6 (2.4%)	2 (1.0%)	6 (1.5%)	5 (1.5%)	20 (2.2%)
Blood and lymphatic system disorders	2 (1.6%)	5 (1.9%)	7 (2.7%)	2 (1.0%)	7 (1.8%)	4 (1.2%)	19 (2.1%)
Anaemia	1 (0.8%)	2 (0.8%)	3 (1.2%)	1 (0.5%)	4 (1.0%)	2 (0.6%)	9 (1.0%)
Eye disorders	4 (3.1%)	7 (2.7%)	8 (3.1%)	3 (1.5%)	4 (1.0%)	7 (2.1%)	19 (2.1%)
Metabolism and nutrition disorders	3 (2.3%)	4 (1.6%)	5 (2.0%)	0 (0.0%)	9 (2.3%)	3 (0.9%)	18 (2.0%)
Cardiac disorders	0 (0.0%)	4 (1.6%)	6 (2.4%)	1 (0.5%)	5 (1.3%)	1 (0.3%)	15 (1.7%)
Renal and urinary disorders	3 (2.3%)	4 (1.6%)	3 (1.2%)	1 (0.5%)	4 (1.0%)	4 (1.2%)	11 (1.2%)
Reproductive system and breast disorders	4 (3.1%)	2 (0.8%)	4 (1.6%)	0 (0.0%)	3 (0.8%)	4 (1.2%)	9 (1.0%)

Table 13: Number of subjects with any adverse events (with frequency of >= 5% occurring in the golimumab group in all studies) through 15 August 2012; treated subjects in RA Phase 3 intravenous studies

	C0524T12[a]			ART3001[b]			
		Golimumab			Golimumab	All Studies	
	Placebo	2 mg/kg q12	4 mg/kg q12	Placebo	2 mg/kg q8	Placebo	Golimumab
Treated subjects in Phase 3 RA intravenous studies[c]	129	259	417	197	584	326	1210
Avg duration of follow up (weeks)	24.4	56.7	60.0	21.0	85.3	22.3	74.0
Avg exposure(number of administrations)	2.9	4.8	5.0	4.2	11.5	3.7	8.3
Subjects with any adverse events	93 (72.1%)	221 (85.3%)	355 (85.1%)	98 (49.7%)	452 (77.4%)	191 (58.6%)	995 (82.2%)
System-organ class/preferred term							
Infections and infestations	52 (40.3%)	129 (49.8%)	224 (53.7%)	48 (24.4%)	286 (49.0%)	100 (30.7%)	629 (52.0%)
Upper respiratory tract infection	12 (9.3%)	36 (13.9%)	58 (13.9%)	15 (7.6%)	67 (11.5%)	27 (8.3%)	157 (13.0%)
Bronchitis	7 (5.4%)	23 (8.9%)	34 (8.2%)	2 (1.0%)	48 (8.2%)	9 (2.8%)	105 (8.7%)
Nasopharyngitis	6 (4.7%)	22 (8.5%)	21 (5.0%)	5 (2.5%)	37 (6.3%)	11 (3.4%)	80 (6.6%)
Urinary tract infection	2 (1.6%)	13 (5.0%)	30 (7.2%)	6 (3.0%)	37 (6.3%)	8 (2.5%)	80 (6.6%)
Sinusitis	6 (4.7%)	15 (5.8%)	31 (7.4%)	3 (1.5%)	19 (3.3%)	9 (2.8%)	63 (5.2%)
Musculoskeletal and connective tissue disorders	27 (20.9%)	84 (32.4%)	109 (26.1%)	31 (15.7%)	123 (21.1%)	58 (17.8%)	311 (25.7%)
Rheumatoid arthritis	7 (5.4%)	31 (12.0%)	32 (7.7%)	12 (6.1%)	46 (7.9%)	19 (5.8%)	106 (8.8%)
Gastrointestinal disorders	33 (25.6%)	86 (33.2%)	122 (29.3%)	17 (8.6%)	103 (17.6%)	50 (15.3%)	307 (25.4%)
Nausea	9 (7.0%)	25 (9.7%)	43 (10.3%)	3 (1.5%)	15 (2.6%)	12 (3.7%)	81 (6.7%)
Diarrhoea	2 (1.6%)	19 (7.3%)	21 (5.0%)	2 (1.0%)	22 (3.8%)	4 (1.2%)	62 (5.1%)
Skin and subcutaneous tissue disorders	11 (8.5%)	60 (23.2%)	65 (15.6%)	9 (4.6%)	70 (12.0%)	20 (6.1%)	195 (16.1%)
Nervous system disorders	20 (15.5%)	48 (18.5%)	67 (16.1%)	12 (6.1%)	69 (11.8%)	32 (9.8%)	182 (15.0%)
Headache	13 (10.1%)	25 (9.7%)	34 (8.2%)	5 (2.5%)	34 (5.8%)	18 (5.5%)	93 (7.7%)
Investigations	18 (14.0%)	38 (14.7%)	58 (13.9%)	12 (6.1%)	86 (14.7%)	30 (9.2%)	180 (14.9%)
Alanine aminotransferase increased	9 (7.0%)	18 (6.9%)	22 (5.3%)	7 (3.6%)	35 (6.0%)	16 (4.9%)	74 (6.1%)

Ex. 2052-027

	C0524T12[a]			ART3001[b]		All Studies	
		Golimumab			Golimumab		
	Placebo	2 mg/kg q12	4 mg/kg q12	Placebo	2 mg/kg q8	Placebo	Golimumab
Respiratory, thoracic and mediastinal disorders	19 (14.7%)	35 (13.5%)	67 (16.1%)	6 (3.0%)	51 (8.7%)	25 (7.7%)	151 (12.5%)
Injury, poisoning and procedural complications	13 (10.1%)	33 (12.7%)	58 (13.9%)	8 (4.1%)	49 (8.4%)	21 (6.4%)	139 (11.5%)
Vascular disorders	9 (7.0%)	31 (12.0%)	35 (8.4%)	7 (3.6%)	53 (9.1%)	16 (4.9%)	119 (9.8%)
Hypertension	5 (3.9%)	22 (8.5%)	20 (4.8%)	5 (2.5%)	38 (6.5%)	10 (3.1%)	80 (6.6%)
General disorders and administration site conditions	11 (8.5%)	32 (12.4%)	45 (10.8%)	7 (3.6%)	35 (6.0%)	18 (5.5%)	112 (9.3%)
Metabolism and nutrition disorders	6 (4.7%)	15 (5.8%)	31 (7.4%)	0	43 (7.4%)	6 (1.8%)	89 (7.4%)
Blood and lymphatic system disorders	3 (2.3%)	12 (4.6%)	21 (5.0%)	4 (2.0%)	42 (7.2%)	7 (2.1%)	74 (6.1%)
Cardiac disorders	1 (0.8%)	9 (3.5%)	23 (5.5%)	1 (0.5%)	35 (6.0%)	2 (0.6%)	67 (5.5%)
Psychiatric disorders	3 (2.3%)	27 (10.4%)	22 (5.3%)	3 (1.5%)	18 (3.1%)	6 (1.8%)	67 (5.5%)
Eye disorders	6 (4.7%)	14 (5.4%)	31 (7.4%)	3 (1.5%)	21 (3.6%)	9 (2.8%)	66 (5.5%)

[a] Study C0524T12 data is through Week 48 database lock. Subjects received golimumab 2 mg/kg or 4 mg/kg every 12 weeks up to Week 48 database lock. Received golimumab with or without MTX. All subjects in placebo group received MTX.
[b] Study ART3001 data is through August 15, 2012. Subjects received golimumab 2 mg/kg at Week 0 and Week 4, and every 8 weeks thereafter. All subjects also received MTX.
[c] Subjects may appear in more than one column.

Overall, the reported AEs during the 16 weeks placebo-controlled period are in line with the expected safety profile of golimumab. Infections and infestations were reported for approximately 30 % of golimumab treated patients across the two i.v. studies. URTI was the most frequently reported infection, with similar frequency in the golimumab and placebo treated groups (6.2 and 6.4%). A similar picture was reported during for the week 24 period; infections being the most commonly reported events with 30.1% for placebo and 32.8% for golimumab groups.

It is noted that there was a difference in the frequencies of reported events in the two studies (e.g. at week 16, 43.7% and 47.3% for placebo and golimumab groups respectively in study 3001, and 67.4% and 65.9% for placebo and golimumab groups, respectively, in study T12), while the pattern of reported AEs is similar. It was concluded that this is due to the fact that these are 2 separate studies performed in different geographic regions.

Review of more detailed presentations of events (line listing submitted by the MAH), shows that for the SOC Nervous system disorders, there was a higher incidence of events, related to the three already labelled terms *Headache*, *Dizziness and Paraesthesia. For and subcutaneous tissue disorders, Rash, Alopecia, Pruritus and urticaria* was increased compared with the placebo group, and all these events are already labelled. Further, in both the week 16 and week 24 data sets, the incidence of vascular events were increased in the overall golimumab group vs. placebo, and there was also a higher incidence of cardiac events in the golimumab groups compared with placebo-group (frequency less than 1%).

The vascular events appear to be mainly related to higher incidence of hypertension, which is a labelled event. For cardiac disorders there was a higher incidence among golimumab treated patients than among those on placebo (e.g. 0.3% placebo and 2.3% for the total golimumab group at week 24). The increase observed consisted was related to various events including 5 events of palpitations and bradycardia each, while none for palcebo. When looking at the integrated Phase 3 RA IV studies, it is noted that the numerical difference between placebo and golimumab-treated patients is remarkably high, 2 vs 67 affected patients. However, figures are difficult to interpret, given that the placebo groups were smaller and the treatment period considerably shorter. The MAH is requested to provide per 100 patient years figures, from study ART 3001 and for study subjects treated with the marketed dose, as well as placebo treated subjects.

Ex. 2052-028

It is also noted that nausea was observed among 3.5% of golimumab treated patients and among 2.5 % in the placebo group (data for week 16); which is an event that has been discussed previously within FUM-procedures.

Through week 16, for psychiatric disorders, there were in total 1.5% events reported for the placebo group compared with 2.2% in the total golimumab group, and among those, there was a higher incidence of depression in the golimumab group with 8 cases (0.9%), compared with 1 (0.3%) in the control group. Depression is labelled as a common event.

Infusion reactions

Table 14: Number of subjects with 1 or more infusion reactions through 15 August 2012 treated subjects in Phase 3 RA intravenous studies

	C0524T12[a]			ART3001[b]		All Studies	
		Golimumab			Golimumab		
	Placebo	2 mg/kg q12	4 mg/kg q12	Placebo	2 mg/kg q8	Placebo	Golimumab
Treated subjects in Phase 3 RA intravenous studies[c]	129	259	417	197	584	326	1210
Avg number of infusions	2.9	4.8	5.0	4.2	11.5	3.7	8.3
Total number of infusions	368	1240	2078	829	6717	1197	10035
Infusions with infusion reactions	7 (1.9%)	21 (1.7%)	17 (0.8%)	2 (0.2%)	30 (0.4%)	9 (0.8%)	68 (0.7%)
Subjects with 1 or more infusion reactions	7 (5.4%)	17 (6.6%)	14 (3.4%)	1 (0.5%)	23 (3.9%)	8 (2.5%)	54 (4.5%)

There was a higher incidence of infusion reactions in golimumab-treated patients when combining all golimumab groups in the two studies. Looking at the different dose levels, both 2 mg/kg groups in the two respective studies, resulted in higher incidences than the respective control groups in these studies. In the 4 mg/kg group in T12, there was a lower incidence compared to the T12 placebo group. It should also be noted that in T12, golimumab was given both in combination with MTX and as monotherapy, while in ART3001 it was only given in combination with MTX, which is the posology applied for.

The general incidence was relatively low (2.6% subjects with at least one infusion reaction for placebo vs. 3.6% for golimumab), and there was one anaphylactic reaction reported, and one case of a severe reaction. Both of these events occurred in the T12 study, although for the severe reactions, it is not clearly stated which treatment this patient had received. This has now been satisfactory clarified, see Day 150 Clinical response assessment report.

When comparing the two studies, a higher incidence of infusion reactions was observed in golimumab-treated versus placebo treated subjects in ART3001 compared with C0524T12. The placebo infusions in ART3001 were 0.9% normal saline, while the placebo infusions in C0524T12 were true matched placebo, including histidine, sorbitol, and polysorbate 80 in aqueous medium at pH 5.5. This could explain the apparent higher placebo-incidences seen in the T12 than in ART3001.

Certain patients had used prophylactic treatment to prevent infusion reactions. No clear recommendations regarding this were made in the protocol, and the MAH does not propose any recommendation about use of prophylactic treatment in section 4.4 of the SPC. This is acceptable, since prophylactic treatment (without corticosteroids) has not been shown to protect against reactions.

All infusions in the studies were given during a 30 min period. This is the recommended infusion time in the proposed SPC, which is accepted, given that the incidences of infusion reactions were relatively low, and that no serious event occurred in association with administration. Nevertheless appropriate labelling is of importance.

Ex. 2052-029

The Applicant provided safety data comparison to relevant subjects in studyC0524T06, see table 16. This study is considered the most relevant study for safety comparison as it enrolled a similar MTX non-responder subject population. This was appreciated and should be elaborated. In the submission, comparisons were also made, however with all participating subjects, regardless of SC dose, see table 16.

Table 15: Key Safety Findings through Week 52 in Studies CNTO148ART3001 and C0524T06

	CNTO148ART3001 (IV)	C0524T06 (SC)
	Golimumab 2 mg/kg + MTX[a]	Golimumab 50 mg + MTX[b]
Subjects treated	584	89
Average duration of administration (weeks)	43.5	45.3
Average exposure (number of administrations)	5.9	11.1
Subjects with adverse events	377 (64.6%)	77 (86.5%)
Subjects with serious adverse events	50 (8.6%)	9 (10.1%)
Subjects who discontinued due to adverse event	21 (3.6%)	4 (4.5%)
Deaths	1	0
Subjects with infections	217 (37.2%)	44 (49.4%)
Subjects with serious infections	11 (1.9%)	2 (2.2%)
Subjects with neoplasms benign, malignant, and unspecified	10 (1.7%)	6 (6.7%)
Total number of infusions/injections	3421	1970
Infusions/injections with reaction	25 (0.7%)	17 (0.9%)
Subjects with 1 or more infusion/injection reaction	21 (3.6%)	7 (7.9%)
Subjects with antibodies to golimumab	26/560 (4.6%)	2/74 (2.7%)

[a] Includes subjects who received at least one golimumab 2 mg/kg dose through Week 52

[b] Includes subjects randomized to SC golimumab 50 mg q4w + MTX. For subjects who met early escape criteria and received golimumab 100 mg q4w + MTX starting at Week 16, the AEs are only counted through Week 16.

Ex. 2052-030

Table 16: Key Safety Findings through Week 112 in Study CNTO148ART3001 and Week 104 in Study C0524T06

	CNTO148ART3001 (IV)	C0524T06 (SC)
	Golimumab Combined	Golimumab Combined
Subjects treated	584	434
Average duration of follow-up (weeks)	95.9	89.9
Average exposure (number of administrations)	11.9	21.6
Subjects with adverse events	462 (79.1%)	388 (89.4%)
Subjects with serious adverse events	106 (18.2%)	98 (22.6%)
Subjects who discontinued due to adverse event	41 (7.0%)	41 (9.4%)
Deaths	5 (0.9%)	4 (0.9%)
Subjects with infections	287 (49.1%)	293 (67.5%)
Subjects with serious infections	36 (6.2%)	29 (6.7%)

The safety concern for this product is not primarily that there may be a safety issues associated to IV administration as such, but rather that the 3 times higher exposure of the drug, necessary to achieve a response that is similar to the currently marketed SC dosing may be associated with increased risks. Therefore, the relevant comparison would be safety data from ART3001 compared to safety data from SC 50mg Q4W in a similar population. However, in study T06, 89 subjects were randomized to 50mg sc Q4W and 178 subjects were randomized to 100mg sc Q4W. After early escape at Week 16 and crossover from placebo at week 24, a total of 212 subjects received at least one dose of 50mg Q4W, whereas 237 received 100mg Q4W.

Ex. 2052-031

Serious adverse events and deaths

Death

Table 17:

Appendix A.19: List of subjects who died after start of study drug administration through 15 August 2012; treated subjects in Phase 3 RA intravenous studies

Indication	Study[a]	Treatment Group[b]	Subject ID	Age (yrs)	Sex	Study Agent Dose Prior to Death	Study Day of Study Agent Administration Prior to Death	Study Day of Death	Cause of Death
RA/IV	ART3001	Placebo + MTX	0113-00083	64	F	2.0 mg/kg	699	746	UNKNOWN AT THIS TIME
			0705-00240	40	F	0.0	141	164	STROKE
			4806-00174	56	M	2.0 mg/kg	533	556	UNKNOWN
		Golimumab 2 mg/kg + MTX	5205-00647	48	F	2.0 mg/kg	197	381	ACUTE ABDOMINAL SYNDROME
			5206-01051	32	F	2.0 mg/kg	198	255	MYOCARDIAL INFARCTION
			6005-00055	57	F	2.0 mg/kg	428	467	SEPTIC SHOCK SECONDARY TO PYOGENIC LUNG ABSCESS
	C0524T12	Golimumab 2 mg/kg + MTX	1004-20786	50	F	2.0 mg/kg	337	370	SEPTIC SHOCK
		Golimumab 2 mg/kg + sham MTX	1023-20485	65	F	1.9 mg/kg	251	354	UNKNOWN
			4020-20253	32	F	2.1 mg/kg	251	323	MYOCARDIAL INFARCTION
		Golimumab 4 mg/kg + MTX	3422-20366	59	M	4.0 mg/kg	253	265	MYOCARDIAL INFARCT
		Golimumab 4 mg/kg + sham MTX	1001-20397	58	F	4.0 mg/kg	253	295	ACUTE MYOCARDIAL INFARCTION
			1010-20415	52	F	4.0 mg/kg	427	458	RESPIRATORY INSUFFICIENCY

[a] Data for C0524T12 is through Week 48 database lock and for ART3001 is through August 15, 2012.
[b] Based on randomized treatment group.

Adapted from: [LSFS1A01.rtf] [CNTO148\Z_SCS\DBR_120DSU_IV_15AUG2012\RE_120DSU_IV_15AUG2012\lsfs1a01.sas] 08OCT2012, 11:26

Table 18:

Appendix A.7: Number of deaths per hundred subject-years of exposure through 15 August 2012; treated subjects in Phase 3 RA intravenous studies

	C0524T12[a]		ART3001[b]	
	2 mg/kg q12	4 mg/kg q12	2 mg/kg q8	All Studies
Golimumab treated subjects in Phase 3 RA intravenous studies[c]	259	417	584	1210
Number of subjects who died	2 (0.8%)	3 (0.7%)	3 (0.5%)	8 (0.7%)
Total subject-years of exposure	281	476	942	1698
Incidence per 100 subject-years	0.71	0.63	0.32	0.47
95% confidence interval[d]	(0.09, 2.57)	(0.13, 1.84)	(0.07, 0.93)	(0.20, 0.93)

[a] Study C0524T12 data is through Week 48 database lock. Subjects received golimumab 2 mg/kg or 4 mg/kg every 12 weeks up to Week 48 database lock. Received golimumab with or without MTX.
[b] Study ART3001 data is through August 15, 2012. Subjects received golimumab 2 mg/kg at Week 0 and Week 4, and every 8 weeks thereafter. All subjects also received MTX.
[c] Subjects may appear in more than one column.
[d] Confidence intervals based on an exact method.

Adapted from: [TSFS1B01B.rtf] [CNTO148\Z_SCS\DBR_120DSU_IV_15AUG2012\RE_120DSU_IV_15AUG2012\TSFS1B01B.sas] 08OCT2012, 22:49

Mortality in RA studies with anti-TNF agents has been assessed in depth within the PhVWP during 2010. It was concluded, that when considering the totality of data, there was no increased risk for mortality associated with anti-TNF agents used for treatment of RA. However, it was noted that the experience for golimumab was limited.

In study T12, there were in total 6 deaths during the initial 24 week period. In the 2 mg/kg q12 week group, there were 3 deaths (1.2% or 1.1/100 pty), while the incidence/100 pty in the 4 mg/kg q12 week was lower (0.7% or 0.62/100 pty) and in the 2 mg/kg Q8 week there was no case among nearly twice as many patients (although with a so far shorter duration of treatment). The reported causes of death are not unexpected for this patient population given anti-TNF + MTX treatment. However, it is somewhat strange that the cause of death is listed as unknown for one case within a clinical study. It is also not understood how this death can be considered by the investigator as unrelated, if the cause of death was unknown. In addition, it is questioned that two cases dying from severe infection or septic shock are non-related given the well known risk for infection associated with the use of golimumab.

Ex. 2052-032

In study CNTO148ART3001 one placebo treated subject died on day 160.
Through 15 August 2012, there were 5 additional deaths. Death causes were peritoneal TB, Clostridium difficile colitis, opportunistic bacterial pneumonia and myocardial infarction (in a 32-year old woman). For the fifth case the cause is unknown.

The incidence of death per 100 subject-years in study ART3001 is somewhat higher than the incidence per 100 subject-years in study T06, 0.53 vs. 0.35, but numbers are small. However, the MAH should summarize and discuss the deaths in both IV studies, vs SC formulation.

Serious adverse events

Table 19: Number of subjects with 1 or more serious adverse events through Week 24; treated subjects in RA Phase 3 intravenous studies.

	C0524T12			ART3001		All Studies	
		Golimumab			Golimumab		
	Placebo	2 mg/kg q12	4 mg/kg q12	Placebo	2 mg/kg q8[a]	Placebo	Golimumab
Treated subjects in RA Phase 3 intravenous studies[b]	129	259	292	197	463	326	1012
Avg duration of follow-up (weeks)	21.4	23.6	21.8	20.9	21.4	21.1	22.1
Avg exposure (number of administrations)	2.6	2.0	1.9	4.2	3.6	3.6	2.7
Subjects with 1 or more serious adverse events	7 (5.4%)	17 (6.6%)	8 (2.7%)	4 (2.0%)	19 (4.1%)	11 (3.4%)	44 (4.3%)
System-organ class/preferred term							
Infections and infestations	2 (1.6%)	8 (3.1%)	3 (1.0%)	0 (0.0%)	3 (0.6%)	2 (0.6%)	14 (1.4%)
Pneumonia	1 (0.8%)	2 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	2 (0.2%)
Appendicitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Arthritis bacterial	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Bacteraemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Cellulitis	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Diverticulitis	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Eye abscess	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Localised infection	1 (0.8%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.1%)
Lower respiratory tract infection	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Osteomyelitis	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Pneumonia bacterial	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)

Ex. 2052-033

	C0524T12			ART3001		All Studies	
		Golimumab			Golimumab		
	Placebo	2 mg/kg q12	4 mg/kg q12	Placebo	2 mg/kg q8[a]	Placebo	Golimumab
Upper respiratory tract infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Urinary tract infection	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Post procedural infection	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	1 (0.8%)	1 (0.4%)	1 (0.3%)	1 (0.5%)	3 (0.6%)	2 (0.6%)	5 (0.5%)
Arthralgia	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Back pain	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Intervertebral disc protrusion	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Osteonecrosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Rheumatoid arthritis	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.2%)	2 (0.6%)	1 (0.1%)
Injury, poisoning and procedural complications	0 (0.0%)	2 (0.8%)	2 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.4%)
Collapse of lung	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Concussion	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Hip fracture	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Synovial rupture	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Renal and urinary disorders	1 (0.8%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	3 (0.6%)	1 (0.3%)	4 (0.4%)
Calculus ureteric	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.3%)	1 (0.1%)
Nephrolithiasis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Nephropathy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Renal colic	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Renal failure	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)

	C0524T12			ART3001		All Studies	
		Golimumab			Golimumab		
	Placebo	2 mg/kg q12	4 mg/kg q12	Placebo	2 mg/kg q8[a]	Placebo	Golimumab
Cardiac disorders	0 (0.0%)	1 (0.4%)	1 (0.3%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	3 (0.3%)
Acute coronary syndrome	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Myocardial ischaemia	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Ventricular tachycardia	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Gastrointestinal disorders	0 (0.0%)	1 (0.4%)	0 (0.0%)	2 (1.0%)	2 (0.4%)	2 (0.6%)	3 (0.3%)
Abdominal pain upper	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Gastric disorder	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Nausea	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Vomiting	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Gastrointestinal haemorrhage	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Inguinal hernia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Nervous system disorders	2 (1.6%)	1 (0.4%)	0 (0.0%)	1 (0.5%)	2 (0.4%)	3 (0.9%)	3 (0.3%)
Cerebral infarction	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Headache	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Ischaemic stroke	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Subarachnoid haemorrhage	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Cerebrovascular accident	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Neuralgia	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Syncope	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	0 (0.0%)	2 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	3 (0.3%)
Interstitial lung disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Pleural effusion	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Pulmonary fibrosis	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)

Ex. 2052-034

	C0524T12			ART3001		All Studies	
		Golimumab					
	Placebo	2 mg/kg q12	4 mg/kg q12	Placebo	Golimumab 2 mg/kg q8[a]	Placebo	Golimumab
Hepatobiliary disorders	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.4%)	0 (0.0%)	2 (0.2%)
Cholecystitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Hepatitis toxic	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Metabolism and nutrition disorders	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	2 (0.2%)
Electrolyte imbalance	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Fluid overload	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.4%)	1 (0.3%)	2 (0.2%)
Breast cancer	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Salivary gland adenoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Basal cell carcinoma	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Reproductive system and breast disorders	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	2 (0.2%)
Endometrial hyperplasia	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Metrorrhagia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Vascular disorders	0 (0.0%)	1 (0.4%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.2%)
Aortic stenosis	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Deep vein thrombosis	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Eye disorders	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Keratitis	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
General disorders and administration site conditions	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Chest pain	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)

	C0524T12			ART3001		All Studies	
		Golimumab					
	Placebo	2 mg/kg q12	4 mg/kg q12	Placebo	Golimumab 2 mg/kg q8[a]	Placebo	Golimumab
Psychiatric disorders	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Depression	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Skin and subcutaneous tissue disorders	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Rash	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)

[a] Received golimumab 2 mg/kg at Week 0 and Week 4, and every 8 weeks thereafter. All subjects also received MTX.
[b] Subjects may appear in more than one column.

Review of SAEs did not reveal any new safety concerns given the well known safety profile of an anti-TNF agent.

Through Week 16 in the integrated Phase 3 RA IV studies, SAEs occurred in 1.2% of placebo-treated subjects and 3.7% of golimumab-treated subjects. The highest incidence of SAEs occurred in the infections and infestations SOC (0.3% placebo, 1.3% golimumab groups). Results for Week 24 are shown above, and were in line with those at week 16.

Through 15 August 2012 in the integrated Phase 3 RA IV studies, SAEs occurred in 16.3% of golimumab-treated subjects. The highest incidence of SAEs occurred in the infections and infestations SOC, and pneumonia, cellulitis (both infections of interest), urinary tract infection (UTI), RA, and osteoarthritis were the most common SAEs.

For malignancy, there is no new safety signal reported in these studies, compared with previous experience from studies with s.c. administration. Risk for malignancy is included in the PI. Section 4.8 lists *Neoplasms (such as skin cancer, squamous cell carcinoma and melanocytic naevus)* as Uncommon and *Lymphoma, leukaemia* as rare events.

There were no cases of demyelination reported, an already labelled event.

Ex. 2052-035

Laboratory findings

Based on pre-sepecified criteria, through Week 16 in the integrated Phase 3 RA IV studies, the only markedly abnormal postbaseline chemistry values reported on more than one occasion in any subject were elevated ALT, elevated glucose, and decreased albumin in 1 golimumab-treated subject each, and decreased glucose in 1 placebo-treated and 1 golimumab-treated subject.

The incidence of ALT elevations was higher in study ART3001 than in study T06. This will be further evaluated when a reanalysis comparing the proposed IV dosing to the currently approved SC dose has been provided.

Safety in special populations

Data in elderly is limited. However, previously, no differences have been seen in the adverse event profile among patients > 65 years and below. However, caution should be exercised when treating the elderly and particular attention paid with respect to occurrence of infections. This is already included in the SPC. Regarding weight, there was a tendency to lower effect in patients above 100 kg of body weight, which is reflected in the s.c. SPC. This should not be a problem here as a weight adjusted posology is applied for.

Immunological events

Table 20: Summary of subjects with positive antibody to golimumab status through Week 24 by dose and MTX use; treated subjects in C0524T12 and CNTO148ART3001 by randomized treatment group.

	Golimumab							
	Received MTX[a]				Did Not Receive MTX[a]			
	Placebo → Golimumab[b]	Golimumab 2 mg/kg	Golimumab 4 mg/kg	Combined Golimumab + MTX	Golimumab 2 mg/kg	Golimumab 4 mg/kg	Combined Golimumab	All Golimumab
Subjects treated in C0524T12	36	129	128	293	127	129	256	549
Subjects with appropriate samples in C0524T12[c]	36	123	122	281	123	125	248	529
Subjects positive for antibodies to golimumab at any time[d]	0 (0.0%)	4 (3.3%)	1 (0.8%)	5 (1.8%)	16 (13.0%)	6 (4.8%)	22 (8.9%)	27 (5.1%)
Subjects treated in CNTO148ART3001	68	395	0	463	0	0	0	463
Subjects with appropriate samples in CNTO148ART3001[c]	67	373	0	440	0	0	0	440
Subjects positive for antibodies to golimumab at any time[d]	0 (0.0%)	13 (3.5%)	0 (NA)	13 (3.0%)	0 (NA)	0 (NA)	0 (NA)	13 (3.0%)
All subjects treated in 2 Phase 3 IV studies	104	524	128	756	127	129	256	1012
All RA subjects with appropriate samples[c]	103	496	122	721	123	125	248	969
Subjects positive for antibodies to golimumab at any time[d]	0 (0.0%)	17 (3.4%)	1 (0.8%)	18 (2.5%)	16 (13.0%)	6 (4.8%)	22 (8.9%)	40 (4.1%)

[a] Use of concomitant MTX was based on the randomized treatment group although MTX could be added due to early escape for subjects who received golimumab monotherapy in C0524T12.
[b] At Week 16, subjects from C0524T12 early escaped to golimumab 4 mg/kg while subjects from CNTO148ART3001 early escaped to golimumab 2 mg/kg.
[c] Subjects with appropriate samples had 1 or more samples obtained after their first study agent administration.
[d] Includes all subjects who had at least 1 positive sample through Week 24.

The overall incidence for antibodies against golimumab was 4.1 % in the phase 3 i.v. studies. Patients treated with monotherapy had approximately 4x higher incidence of antibodies than those treated with MTX (8.9% vs. 2.5%). Further, in T12, there was also a difference between doses, where the 4 mg/kg

Ex. 2052-036

dose resulted in lower incidences. The 2 mg/kg monotherapy group had the highest incidence (13%). As currently approved for s.c. use, also the i.v. indication applied for corresponds to combination therapy with MTX, which will reduce the occurrence for antibody development compared with monotherapy.

During the 24 week period, for golimumab-treated subjects in the integrated Phase 3 RA IV studies, 1 of 40 subjects (2.5%) were positive for antibodies to golimumab and experienced an infusion reaction compared with 39 of 929 subjects (4.2%) who were negative for antibodies to golimumab and experienced an infusion reaction. None of these golimumab treated subjects experienced a severe or serious infusion reaction though one golimumab-treated subject out of 929 negative for antibodies to golimumab (0.1%) had a non-severe or non-serious infusion reaction that led to the discontinuation of study agent in Study C0524T12. It is not possible to draw definite conclusions regarding the contribution of antibodies against golimumab to occurrence of infusion reactions, due to the small number of patients positive for antibodies to golimumab.

Safety related to drug-drug interactions and other interactions

No new data provided.

Discontinuation due to AES

Discontinuation of study agent was required per protocol for the following AEs: anaphylactic and serum sickness-like reactions, opportunistic infections, malignancies (excluding NMSC), pregnancy in a subject, congestive heart failure, demyelinating disease, and active TB.

Through Week 16 in the integrated Phase 3 RA IV studies, 0.6% of placebo-treated subjects and 1.9% of golimumab-treated subjects discontinued study agent due to an AE. Through Week 24, worsening of RA was the most common AE leading to discontinuation of study agent (0.5% in the golimumab group). Through the last IV dose, 1.8% of placebo-treated subjects and 5.5% of golimumab-treated subjects discontinued study agent due to an AE. The highest incidence of AEs leading to discontinuation of study agent occurred in the infections and infestations SOC (0.6% and 1.7% in the placebo and golimumab groups, respectively) and musculoskeletal and connective tissue disorders SOC (0.6% and 1.1% in the placebo and golimumab groups, respectively). Worsening of RA was the most common AE leading to discontinuation of study agent (0.3% in the placebo group and 0.9% in the golimumab group). Overall, there are no particular concerns revealed by the data on discontinuations.

Discussion on clinical safety

The safety profile of golimumab is well characterised. Risks associated with treatment include serious infections including opportunistic infections, TB and Hepatitis B viral reactivation, demyelinating disorders, hypertension; lymphoma and other malignancies, CHF, autoimmune processes (SLE or lupus-like syndrome), haematologic reactions, and risk for serious systemic hypersensitivity (including anaphylactic reaction).

With this application, safety and efficacy data from study CNTO148ART3001 has been provided, and the MAH has compared safety data from an RA SC study with safety data provided from study ART 3001. Also, a document addressing patient categories who would benefit from IV Simponi has been submitted.

A PK modelling investigating safety profiles at different quartiles of exposure has been provided, which is mainly assessed in the PK AR.

Ex. 2052-037

An open-label study (P06129) has been included in order to provide data for switching SC to IV/SC.

Overall, the reported AEs during the 16 weeks placebo-controlled period are in line with the expected safety profile of golimumab. Infections and infestations were reported for approximately 30 % of golimumab treated patients across the two i.v. studies. URTI was the most frequently reported infection, with similar frequency in the golimumab and placebo treated groups (6.2 and 6.4%). A similar picture was reported during for the week 24 period; infections being the most commonly reported events with 30.1% for placebo and 32.8% for golimumab groups.

The MAH has with this submission also provided safety data from the pivotal study (CNTO148ART3001) through week 112. For integrated analyses safety data through 15 August 2012 (after all subjects completed at least 52 weeks) are included from this study.

Review of more detailed presentations of events (line listing submitted by the MAH), shows that for the SOC Nervous system disorders, there was a higher incidence of events, related to the three already labelled terms *Headache*, *Dizziness and Paraesthesia. For and subcutaneous tissue disorders, Rash, Alopecia, Pruritus and urticaria* was increased compared with the placebo group, and all these events are already labelled. Further, in both the week 16 and week 24 data sets, the incidence of vascular events were increased in the overall golimumab group vs. placebo, and there was also a higher incidence of cardiac events in the golimumab groups compared with placebo-group (frequency less than 1%). The vascular events appear to be mainly related to higher incidence of hypertension, which is a labelled event. For cardiac events the numerical difference between placebo and golimumab-treated patients that experienced cardiac events is remarkably high, 2 vs 67 affected patients. However, figures are difficult to interpret, given that the placebo groups were smaller and the treatment period considerably shorter. The MAH is requested to provide per 100 patient years figures, from study ART 3001 and for study subjects treated with the marketed dose, as well as placebo treated subjects.

It is also noted that nausea was observed among 3.5% of golimumab treated patients and among 2.5 % in the placebo group (data for week 16); which is an event that has been discussed previously within FUM-procedures.

Through week 16, for psychiatric disorders, there were in total 1.5% events reported for the placebo group compared with 2.2% in the total golimumab group, and among those, there was a higher incidence of depression in the golimumab group with 8 cases (0.9%), compared with 1 (0.3%) in the control group. Depression is labelled as a common event.

Mortality in RA studies with anti-TNF agents has been assessed in depth within the PhVWP during 2010. It was concluded, that when considering the totality of data, there was no increased risk for mortality associated with anti-TNF agents used for treatment of RA. However, it was noted that the experience for golimumab was limited. The data from these two IV studies increase the safety database for golimumab.

In study T12, there were in total 6 deaths during the initial 24 week period, while no death was reported among golimumab treated subjects in study ART3001 during the initial W 24 period, despite a more frequent administration. Through 15 August 2012, there were 5 additional deaths in the ART3001 study It is noted that all subjects were less than 65 years old, and that the death causes were peritoneal TB, Clostridium difficile colitis, opportunistic bacterial pneumonia and myocardial infarction (in a 32-year old woman). It is noted that the known causes of death in the ART3001 study point to an involvement of TNF α inhibition.

Ex. 2052-038

The incidence of death per 100 subject-years in study ART3001 is somewhat higher than the incidence per 100 subject-years in study T06 0.52 vs 0.35, but numbers are small (5 deaths in study ART3001 and 4 in the T06 study).The MAH should discuss the incidence difference, and the character of the cases, providing narratives on the cases from T06.The reported causes of death are not unexpected for this patient population given anti-TNF + MTX treatment.

Detailed review of the various events of infections that have been reported in the phase 3 RA studies does not reveal any new safety concerns given the well known safety profile of an anti-TNF agent.. The various events of infections that have been reported in the phase 3 RA studies are consistent with the known safety profile of an anti-TNF agent.

In the CNTO148ART3001 study, 4 subjects experienced opportunistic infections through´15 August 2012. In the C0524T12 study, 3 subjects experienced opportunistic infections through the last IV dose. The incidence of opportunistic infections per 100 subject-years of follow-up in golimumab treated subjects through 15 August 2012 in the integrated Phase 3 RA IV studies was 0.41 (CI:0.16, 0.84). For study T06, the incidence per 100 subject-years was 0,27 (CI:0.05-0.78).

For malignancy, there is no new safety signal reported in these studies, compared with previous experience from studies with s.c. administration. Risk for malignancy is included in the PI. Section 4.8 lists *Neoplasms (such as skin cancer, squamous cell carcinoma and melanocytic naevus)* as Uncommon and *Lymphoma, leukaemia* as rare events.

There were no cases of demyelination reported, an already labelled event.

There was a higher incidence of <u>infusion reactions</u> in golimumab-treated patients when combining all golimumab groups in the two studies. Looking at the different dose levels, both 2 mg/kg groups in the two respective studies, resulted in higher incidences than the respective control groups in these studies. In the 4 mg/kg group in T12, there was a lower incidence in compared with the T12 placebo group. It should also be noted that in T12, golimumab was given both in combination with MTX and as monotherapy, while in ART3001 it was only given in combination with MTX, which is the posology applied for. The placebo infusions in ART3001 were 0.9% normal saline, while the placebo infusions in C0524T12 were true matched placebo, including histidine, sorbitol, and polysorbate 80 in aqueous medium at pH 5.5. This could explain the apparent higher placebo-incidences seen in the T12 than in ART3001.

Through Week 16 in study C0524T12, prophylactic treatment was administered prior to at least one infusion to 128 of 642 treated subjects and to 49 of 592 treated subjects in study CNTO148ART3001. In both studies, the number of infusion reactions in golimumab-treated subjects receiving prophylactic medication was not clinically different than in subjects not receiving prophylactic treatment. Therefore the MAH states that no recommendation on prophylactic treatment to prevent infusion reactions can be made. This is agreed to.

All infusions in the studies were given during a 30 min period. This is the recommended infusion time in the proposed SPC, which is accepted, given the data for infusion reactions.

Regarding hepatobiliary events, through Week 16 in the Phase 3 RA IV studies, 1 subject (4803-00434) in the golimumab 2 mg/kg q8w group in ART3001 had a hepatobiliary AE of ALT >3x ULN with an associated SAE in the hepatobiliary SOC. This subject, who received TB prophylaxis (INH), had an ALT > 8 x ULN and an SAE of toxic hepatitis. No additional clinically important hepatobiliary AEs were through the last IV dose in the Phase 3 RA IV studies. Increased ALT/AST were also reported, in line

Ex. 2052-039

with what is already labelled for Simponi. Elevated ALT and AST are already labelled. In addition, as uncommon events, *cholelithiasis* and *hepatic disorders* are listed. It is not considered that the event described above warrant change of the SPC. However, there is a clear tendency to more hepatic events in the IV study, as compared to study T06, which is not alarmingly high, but may indicate a difference in the safety profile for higher exposure.

In the absence of a SC 50mg Q4W arm in study ART3001, a between studies comparison was made in order to investigate any safety issues. Standard analyses of AEs for CNTO148ART3001 (through Week 112) and C0524T06 (through Week 104) were compared. In addition, the incidence of targeted events was compared for CNTO148ART3001 (through 15 August 2012) and C0524T06 (through Week 160).However, the main safety concern for this product is not that there may be a safety issues associated to IV administration as such, but rather that the 3 times higher exposure of the drug may be associated with increased risks. Therefore the safety comparison should have been made between the currently marketed SC dose, and the proposed IV dose, as well as between the two studied SC doses.

Selected safety events were evaluated in relation to SC and IV golimumab pharmacokinetic (PK) exposure parameters. The proportions of subjects who experienced infections, serious infections or SAEs were assessed by 4 quartile subgroups of increasing PK exposure (Cavg, Cmax, Cmin, and AUC). Another analysis included the distribution of PK exposure versus the occurrence of safety events (0 events, 1 event, >1 events) in subjects who experienced these AEs through Week 52/Week 48. No trend of increasing incidence of safety events were seen for Cavg and Cmin for the combined data. Further, when comparing SC only and IV only data, there was also no trend of increased occurrence of safety events with higher systemic exposures. For malignancies, the distribution of PK exposure (Cavg, Cmax, Cmin and AUC) versus the occurrence of malignancies (0=no; 1=yes) were plotted for subjects who had malignancies through the 15 August 2012 cut-off date. From this analysis it was observed that there was no difference in any of the PK exposure metrics for subjects who experienced no malignancies versus subjects who experienced malignancies. However, since the occurrence (IV and SC combined) of serious infections and malignancies is rather low, 0.5% and 2%, respectively, firm conclusions regarding the distribution of exposure cannot be drawn.

There were no additional concerns identified by the laboratory analyses undertaken.

Regarding the presentation of ADRs in the Product Information (PI):

The methodology used to review the golimumab safety database was consistent with that used previously during the initial MAA review process, and agreed upon with the Rapporteur. ADR frequency was determined in one of 2 ways:

1. Integrated data from the 16-week pure placebo controlled portions of the Phase 3 SC studies in RA, PsA, and AS and the Phase 3 RA IV studies were used to determine the frequencies of most ADRs.
2. If the ADR did not occur during the common placebo-controlled portion of the studies, the frequencies were determined by using longer-term data. These data included up to 160 weeks of the Phase 2b and Phase 3 RA, PsA, AS studies: C0524T02, C0524T05 (Week 160); C0524T06 (Week 160); C0524T11 (Week 160); C0524T08 (Week 160), and C0524T09 (Week 160), Phase 2b asthma study (C0524T03), and Phase 3 RA IV studies (data through 15 June 2011). ADRs determined using this method were: demyelinating disorders, vasculitis (cutaneous and systemic), opportunistic infections, septic shock, hepatitis B reactivation, leukemia, pancytopenia, allergic

Ex. 2052-040

reactions, congestive heart failure, lupus, sarcoidosis, as well as a laboratory finding: autoantibody positive.

Since autoantibody positive is not an AE, but rather a laboratory result, tables for the 5 SC and 2 IV studies were used to calculate incidence and determine this laboratory finding frequency.

Overall, the ADRs that changed frequencies included: tuberculosis, pyelonephritis, infective bursitis (from uncommon to rare); pancytopenia (from rare to uncommon); autoantibody positive (from common to very common); interstitial lung disease (from rare to uncommon); constipation (from common to uncommon); stomatitis (from uncommon to common); renal disorders (from rare to uncommon); impaired healing (from common to rare). This has been reflected in the revised SPC proposed within this application, and is agreed.

In the two studies of i.v. administration, no new safety concerns have been identified. However, when comparing to the s.c administration, this new route will result in a higher systemic exposure during the treatment interval both due to a higher total dose (e.g. for a 75 kg person, the total dose given i.v. during the first 12 weeks will be 450 mg, while for s.c. it will be 200 mg), and since the bioavailability after s.c. administration is lower (approx. 50% bioavailability). Based on the available safety data, it is not possible to with certainty assess whether there is a quantitative difference in the safety profile between the i.v. and s.c. route of administration or not, but a higher risk for adverse effects cannot be excluded. Thus, there is a need to gain more data to assess this further. The MAH should address how data to assess the safety profile of the i.v. formulation further can be obtained in the post marketing setting.

Conclusions on clinical safety

Overall, no new safety signals that warrant an update of the SPC were revealed in the two phase 3 i.v. studies. There are certain points which need to be addressed, in particular the comparison between IV and SC distribution. (See Benefit/Risk assessment and LoQ).

Pharmacovigilance system

The applicant has not provided the required summary of the pharmacovigilance system in accordance with Article 8(3)(ia) of Directive 2001/83/EC.

The summary of the pharmacovigilance system should be provided in module 1.8.1 of the application and includes the following elements:

- proof that the applicant has at its disposal a qualified person responsible for pharmacovigilance;
- the Member States in which the qualified person resides and carries out his or her tasks;
- the contact details of the qualified person;
- a statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in title IX of Directive 2001/83/EC;
- a reference to the location where the pharmacovigilance-system master file (PSMF) for the medicinal product is kept.

The applicant may combine this information in one single statement using the required statement as per Article 8(3)(ia): 'the applicant has the necessary means to fulfil the tasks and responsibilities listed in title IX of Directive 2001/83/EC, signed by the applicant and qualified person for pharmacovigilance (QPPV).

If available, the PSMF number (MFL EVCODE) assigned by the extended EudraVigilance Medicinal Product Dictionary (XEVMPD) should be included in the statement in module 1.8.1

Ex. 2052-041

Risk management plan

Issues and/or concerns for consideration by the PRAC Rapporteur when assessing the RMP:

PRAC Advice

The CHMP received the following PRAC advice on the submitted Risk Management Plan:

The PRAC considered that the risk management system version could be acceptable with revisions required as described in the attached PRAC endorsed PRAC Rapporteur assessment report.

The CHMP endorsed this advice without changes.

Safety concerns

The MAH identifies the following safety concerns

Table 1: Summary of safety concerns

Summary of safety concerns	
• Important identified risks	• Serious infections including opportunistic infections and TB • Demyelinating disorders • Hypertension • Lymphoma • Hepatitis B virus reactivation • Congestive heart failure • Autoimmune processes • Haematologic reactions • Serious systemic hypersensitivity (including anaphylactic reaction) • Vasculitis • Psoriasis (new onset or worsening of pre-existing) • Melanoma
Important potential risks	• Malignancy (excluding lymphoma and melanoma) • Serious hepatotoxicity • Exposure during pregnancy • Serum sickness • Maladministration/administration error • Serious depression including suicidality • Sarcoidosis/sarcoid-like reaction
Missing information	• Use in paediatric patients

Ex. 2052-042

Summary of safety concerns	
	• Use in patients with hepatic impairment • Use in patients with renal impairment • Use in patients with a past history of latent or active TB • Use in patients with concurrent malignancy or a history of malignancy • Use in patients with active infections including HIV, hepatitis B, hepatitis C • Use in patients with recent prior use of other biologics excluding anti-TNFα agents • Use in patients with concomitant diagnosis of CHF including medically controlled asymptomatic CHF • Use in patients with history of demyelinating disease • Use in patients with a history of lupus or lupus-like syndrome • Use in patients after recent vaccination with live bacterial or viral vaccine • Long-term safety data

Having considered the updated data in the safety specification the PRAC considers that long term safety at IV administration should be specifically mentioned as missing information.

Pharmacovigilance plan

Table 2: Ongoing and planned studies in the PhV development plan

Activity / Study title (type of activity, study title [if known] category 1-3)*	**Objectives**	**Safety concerns addressed**	**Status Planned, started,**	**Date for submission of interim or final reports (planned or actual)**
P04480 (noninterventional cohort, category 3)	Evaluate the long term safety of biologics. A minimum follow-up period of 5 years is planned in golimumab (SC and IV)	Serious infections including opportunistic infections and TB Demyelinating disorders Lymphoma Congestive heart failure Haematologic reactions Serious systemic hypersensitivity (including anaphylactic reaction) Melanoma	Ongoing	Interim reports: planned annually Final report: December 2018

Ex. 2052-043

Activity / Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
		Malignancy (excluding lymphoma and melanoma) Serum sickness Long-term safety		
CNTO148ART4003 (noninterventional cohort, category 3)	Using Swedish National (whole population) medical and pharmaceutical data sets to collect characteristics, disease features, adverse events, and serious adverse events of RA, PsA, and AS patients treated with golimumab, other biologics or non-biologics to allow physicians to gain a better understanding of the relative risks and/or any treatment outcomes of golimumab (SC and IV) therapy by indication.	Serious infections including opportunistic infections and TB Demyelinating disorders Hypertension Lymphoma Hepatitis B virus reactivation Congestive heart failure Autoimmune processes Haematologic reactions Serious systemic hypersensitivity (including anaphylactic reaction) Vasculitis Psoriasis (new onset or worsening of pre-existing) Melanoma Malignancy (excluding lymphoma and melanoma Serious hepatotoxicity Serious depression including suicidality Sarcoidosis/ sarcoid-like reaction Use in patients with hepatic impairment Use in patients with renal impairment Use in patients with a past history of latent or active TB Use in patients with concurrent malignancy or a history of malignancy Use in patients with active infections including HIV, hepatitis B, hepatitis C Use in patients with recent	Ongoing	Interim reports: planned annually Final report: February 2016

Ex. 2052-044

Activity / Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
		prior use of other biologics excluding anti- TNFα agents Use in patients with concomitant diagnosis of CHF including medically controlled asymptomatic CHF Use in patients with a history of demyelinating disease Use in patients with a history of lupus or lupus like syndrome Long-term safety data		
CNTO148ART4002 (noninterventional cohort, category 3)	Using a large US health insurance claims database to evaluate the incidence rate of selected outcomes of interest in a cohort of patients with RA, PsA, or AS initiating golimumab, other biologics or nonbiologics. The risks in the golimumab cohort will be compared to those in similar patients in the control cohorts.	See study CNTO148ART4003	Ongoing	Interim reports: Planned annually after 1000 patient years have been accrued in the SIMPONIexposed RA cohort. Final report: September 2018
CNTO148ART4001 (noninterventional cohort category 3)	Using the Swedish, Danish, and Finnish medical birth registers to collect and analyse information pertaining to pregnancy outcomes of women exposed to golimumab during	Exposure during pregnancy	Ongoing	Interim reports planned annually Final report: February 2017

Ex. 2052-045

Activity / Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
	pregnancy and the health status during the first year following delivery of their infants, relative to the background risk in patients treated with other biologics, nonbiologic systemic therapy, and general population controls.			
C0524T05 (RA); (randomised, controlled, category 3)	Assess the efficacy of golimumab in subjects with active RA who have not been previously treated with MTX as measured by 1) reduction of the signs and symptoms of RA at Week 24 and 2) inhibition of progression of structural damage at Week 52. Additionally, to assess the safety of golimumab, the effect of golimumab on physical function and quality of life, and the pharmacodynamics, and population pharmacokinetics of golimumab in subjects with active RA who have not been previously treated with MTX.	Long-term safety data	Ongoing	Final report: December 2013
C0524T06 (RA) (randomised,	Assess the efficacy of golimumab in	Long-term safety data	Ongoing	Final report: December

Ex. 2052-046

Activity / Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
controlled, category 3)	subjects with active RA despite MTX therapy as measured by the reduction of the signs and symptoms of RA at Week 14 and improvement in physical function at Week 24. Additionally, to assess the safety, the effects of golimumab on structural damage and quality of life, and the population pharmacokinetics of golimumab in subjects with active RA despite MTX therapy.			2013
C0524T11 (RA). (randomised, controlled, category 3)	Evaluate the efficacy of golimumab in subjects with active RA who have been previously treated with biologic anti-TNFα agent(s) by assessing reduction in signs and symptoms of RA at Week 14. In addition, to assess the safety, physical function, pharmacodynamics, and population pharmacokinetics of golimumab in subjects with active RA who have been previously treated	Long-term safety data	Ongoing	Final report: December 2013

Ex. 2052-047

Activity / Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
	with biologic anti-TNFα agent(s).			
C0524T08 (PsA) (randomised, controlled, category 3)	Evaluate the efficacy of SC injections of golimumab in subjects with active PsA by assessing reduction in signs and symptoms of PsA and inhibition of progression of structural damage. Evaluate the efficacy of golimumab in: 1) achieving sustained arthritis response, 2) improving psoriatic skin lesions, 3) improving physical function, and 4) improving quality of life; and to assess the safety of golimumab in subjects with active PsA.	Long-term safety data	Completed	Final report: December 2013
C0524T09 (randomised, controlled, category 3)	Assess the efficacy of SC injections of golimumab in subjects with active AS, as measured by reduction in the signs and symptoms of active AS at Week 14. Additionally, to assess 1) the overall safety of golimumab, 2) the effects of golimumab on physical function, range of motion, structural damage,	Long-term safety data	Completed	Final report: December 2013

Ex. 2052-048

Activity / Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
	and quality of life in subjects with AS, and 3) the population pharmacokinetic and pharmacodynamic effects of golimumab in subjects with AS.			
CNTO148JIA3001, (randomised, controlled, category 3)	Assess the clinical efficacy of SC administration of golimumab in paediatric subjects (ages 2 to less than 18 years) with JIA manifested by ⩾5 joints with active arthritis despite methotrexate (MTX) therapy for ⩾ 3 months. Additionally, to evaluate golimumab in paediatric subjects with JIA with respect to: Safety Physical function. Quality of life Disease activitystatus over time Pharmacokinetics and immunogenicity Pharmacodynamics	Use in paediatric patients	Ongoing	April 2016

*Category 1 are imposed activities considered key to the benefit risk of the product.

Category 2 are specific obligations

Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC, having considered the updated data submitted, is of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product, since IV formulation is added to study P4480 and ART4003. It is of importance that safety data from these studies are presented both pooled and by administration route.

Ex. 2052-049

Risk minimisation measures

Table 3: Summary table of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important identified risk	For **all** risks: Medicinal product subject to restricted medical prescription. Simponi treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis	
Serious infections including opportunistic infections and TB	The SmPC contraindicates the use of golimumab in patients with active TB or other severe infections such as sepsis, and opportunistic infections Serious infections including opportunistic infections and TB are specifically addressed in the Contraindications (4.3), Special Warnings and Precautions for Use (4.4), and Undesirable Effects (4.8) sections of the SmPC.	• Patient Alert Card • Golimumab Educational Programme
Demyelinating disorders	Addressed in the Special Warnings and Precautions for Use (4.4), and Undesirable Effects (4.8) sections of the SmPC	The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk. Therefore, no additional risk minimisation activities are proposed.
Hypertension	Addressed in the Undesirable Effects (4.8) section of the SmPC.	The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk. Therefore, no additional risk minimisation activities are proposed.
Lymphoma	Addressed in the Special Warnings and Precautions for Use (4.4), and Undesirable Effects (4.8) sections of the SmPC	The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk. Therefore, no additional risk minimisation activities are proposed.
Hepatitis B virus reactivation	Addressed in the Special	Patient Alert Card

Ex. 2052-050

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Warnings and Precautions for Use (4.4), and Undesirable Effects (4.8) sections of the SmPC. Guidance is provided on monitoring for hepatitis B infection as well as the management of hepatitis B infection.	Golimumab Educational Programme
Congestive heart failure	The SmPC contraindicates the use of golimumab in patients with moderate or severe heart failure (NYHA class III/IV) Addressed in the Special Warnings and Precautions for Use (4.4), and Undesirable Effects (4.8) sections of the SmPC Guidance is provided for patients with mild heart failure (NYHA class I/II) and new or worsening symptoms of heart failure.	Patient Alert Card Golimumab Educational Programme
Autoimmune processes	Addressed in the Special Warnings and Precautions for Use (4.4), and Undesirable Effects (4.8) sections of the SmPC.	The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk. Therefore, no additional risk minimisation activities are proposed.
Haematologic Reactions	Addressed in the Special Warnings and Precautions for Use (4.4), and Undesirable Effects (4.8) sections of the SmPC.	The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk. Therefore, no additional risk minimisation activities are proposed.
Serious systemic hypersensitivity (including anaphylactic reaction)	The SmPC contraindicates the use of golimumab in patients with hypersensitivity to golimumab or to any of the excipients and provides medical advice on how to deal with these reactions. Addressed in the Special Warnings and Precautions for	Golimumab Educational Programme

Ex. 2052-051

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Use (4.4), and Undesirable Effects (4.8) sections of the SmPC.	
Vasculitis	Included in the Undesirable Effects (4.8)section of the SmPC.	The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk. Therefore, no additional risk minimisation activities are proposed.
Psoriasis (new onset or worsening of pre-existing)	Included in the Undesirable Effects (4.8)section of the SmPC.	The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk. Therefore, no additional risk minimisation activities are proposed
Melanoma	Addressed in the Special Warnings and Precautions for Use (4.4), and Undesirable Effects (4.8) sections of the SmPC. Guidance about the overall risk of malignancy, including the need to perform periodic skin examinations is provided in the Special Warnings and Precautions for Use (4.4) section of the SmPC.	Golimumab Educational Programme
Important potential risks		
Malignancy (excluding lymphoma and melanoma)	Guidance about the overall risk of malignancy, including paediatric malignancy and Merkel cell carcinoma, is provided in the Special Warnings and Precautions for Use (4.4) and Undesirable Effects (4.8) sections of the SmPC. Guidance about the need to perform periodic skin examinations for Merkel cell carcinoma is provided in the Special Warnings and Precautions for Use (4.4) section of the SmPC.	The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk. Therefore, no additional risk minimisation activities are proposed Merkel Cell carcinoma: Golimumab Educational Programme
Serious hepatotoxicity	Included in the Undesirable	The Sponsor considers that

Ex. 2052-052

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Effects (4.8)section of the SmPC.	the language included in the SmPC is sufficient to minimise the risk. Therefore, no additional risk minimisation activities are proposed
Exposure during pregnancy	Guidance is provided in the Fertility, Pregnancy, and Lactation (4.6) section of the SmPC.	The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk. Therefore, no additional risk minimisation activities are proposed
Serum sickness	Guidance on serious systemic hypersensitivity reactions, including serum sickness, is provided in the Contraindications (4.3), Special Warnings and Precautions for Use (4.4), and the Undesirable Effects (4.8) sections of the SmPC.	Golimumab Educational Programme
Maladministration/administration error	Detailed instructions on the proper technique of administering golimumab to minimise the risk of injury and assure proper drug delivery is provided in the Posology (4.2) and Method of Administration and Special Precautions for Disposal and Other Handling (6.6) sections of the SmPC, and the Instruction for Use section of the Package Leaflet	Golimumab Educational Programme
Serious depression including suicidality	Included in the Undesirable Effects (4.8)section of the SmPC.	The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk. Therefore, no additional risk minimisation activities are proposed
Sarcoidosis/sarcoid-like reaction	Included in the Undesirable Effects (4.8)section of the SmPC.	The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk.

Ex. 2052-053

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
		Therefore, no additional risk minimisation activities are proposed
Missing information		
Use in paediatric patients	The Posology and Method of Administration (4.2) section in the SmPC indicates that safety in patients less than 18 years of age has not yet been established. The Special Warnings and Precautions for Use (4.4) section provides information about the risk of malignancy in paediatric patients	The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk. Therefore, no additional risk minimisation activities are proposed
Use in patients with hepaticimpairment	This safety concern is included in the Special Warnings and Precautions for Use (4.4) section of the SmPC.	The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk. Therefore, no additional risk minimisation activities are proposed
Use in patients with renal impairment	This safety concern is included in the Special Warnings and Precautions for Use (4.4) section of the SmPC.	The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk. Therefore, no additional risk minimisation activities are proposed
Use in patients with a past history of latent or active TB	Guidance is provided in the Contraindications (4.3), and 4. Special Warnings and Precautions for Use (4.4) sections of the SmPC.	The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk. Therefore, no additional risk minimisation activities are proposed
Use in patients with concurrent malignancy or a history of malignancy	This safety concern is included in the Special Warnings and Precautions for Use (4.4) section of the SmPC.	The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk. Therefore, no additional risk minimisation activities are proposed
Use in patients with active	Guidance is provided in the	The Sponsor considers that

Ex. 2052-054

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
infections including HIV, hepatitis B, hepatitis C	Contraindications (4.3), and Special Warnings and Precautions for Use (4.4) sections of the SmPC.	the language included in the SmPC is sufficient to minimise the risk. Therefore, no additional risk minimisation activities are proposed
Use in patients with recent prior use of other biologics excluding anti-TNFα agents	Guidance is provided in the Special Warnings and Precautions for Use (4.4) and the Interactions with Other Medicinal Products and Other Forms of Interaction (4.5) sections of the SmPC	The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk. Therefore, no additional risk minimisation activities are proposed
Use in patients with concomitant diagnosis of CHF including medically controlled asymptomatic CHF	Guidance is provided in the Contraindications (4.3), and Special Warnings and Precautions for Use (4.4) sections of the SmPC.	The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk. Therefore, no additional risk minimisation activities are proposed
Use in patients with history of demyelinating disease	This safety concern is included in the Special Warnings and Precautions for Use (4.4) section of the SmPC.	The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk. Therefore, no additional risk minimisation activities are proposed
Use in patients with a history of lupus or lupus-like syndrome	This safety concern is included in the Special Warnings and Precautions for Use (4.4) section of the SmPC.	The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk. Therefore, no additional risk minimisation activities are proposed
Use in patients after recent vaccination with live bacterial or viral vaccine	Guidance is provided in the Special Warnings and Precautions for Use (4.4), Interactions with Other Medicinal Products and Other Forms of Interaction (4.5), and Fertility, Pregnancy, and Lactation (4.6) sections of the SmPC.	The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk. Therefore, no additional risk minimisation activities are proposed

Ex. 2052-055

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Long-term safety data	None proposed	None proposed

The PRAC, having considered the updated data submitted, was of the opinion that the proposed risk minimisation measures remains sufficient to minimise the risks of the product in the proposed indications addressed in this version.

4. Orphan medicinal products

N/A

5. Benefit risk assessment

Benefits

Beneficial effects

The results from study CNTO148ART3001 show that the proposed dosing of IV golimumab is effective compared to placebo. There was a larger proportion of ACR 20 responders (primary endpoint) at Week 14 in the golimumab + MTX treatment group compared with the placebo + MTX group; 58.5% of the golimumab treated group achieved ACR 20 response as compared to 24.9% in the placebo group, the difference being 33.6% ($p<0.001$). The 4 major secondary endpoints, Proportion of Subjects With DAS28 Response, Change in Baseline From HAQ-DI at Week 14 ACR 50 Response at Week 24 and change in Baseline in van der Heijde Modified Sharp Score at Week 24 were also met. The results appear to be maintained through weeks 52 and 100, with approximately 69% ACR20 responders and 84% DAS28 responders at Week 100 among golimumab randomized subjects.

Change in Baseline in van der Heijde Modified Sharp Score at Week 24 has been analyzed and shows a positive effect on structural damage, since the change from baseline in vdH-S score at Week 24 was significantly greater in the subjects receiving placebo +MTX than in the subjects receiving IV golimumab + MTX.

The posology applied for is sufficiently supported by the results from study T12 and 3001.

Uncertainty in the knowledge about the beneficial effects

The effects of the IV formulation relative to placebo compares well with the effects demonstrated for the sc formulation (study T06 which was undertaken in a similar population as the main IV study, although with a lower disease activity). However, due to the lack of direct comparison with SC administration it is still not possible to evaluate whether the IV administration provides any efficacy advantages, e.g. time to onset of effect and effect size.

Information regarding switching between the formulations has been provided. Data on subjects who switched from IV to SC formulation are available as part of studyC0524T12 and data from the SC to IV/SC strategy are available as part of study P06129. The MAH concludes that there is insufficient information to give precise guidance to the prescriber. Instead wording is proposed for the SPC, that there is insufficient information about switching between IV and SC administration. This should be further discussed including a proposal for wording for the PI addressing safety aspects when switching between formulations.

Ex. 2052-056

There is a trend towards higher risk of developing antibodies after 24 weeks on IV treatment. No case was found in the SC T06 study after 24 weeks, although it should be noted that this cohort was smaller (141 treated subjects, whereof 137 subjects with appropriate samples, as compared to study ART3001 463 treated subjects, whereof 435 subjects with appropriate samples). This tendency remains at Weeks 52 and 100, where the overall incidences for antibodies to golimumab in ART3001 were 4.6% and 6.7% respectively. At week 52 in the T06 study, 1.1% in the combined SC golimumab + MTX group had developed antibodies to golimumab (no data are available for week 100). A trend towards a weakened response in antibody positive patients at Week 100 in study ART3001 is shown, with 51.4% ACR20 response and 29.7% ACR 50 response for antibody positive subjects, as compared to 70.3% and 45.9% respectively for antibody negative subjects.

Risks

Unfavourable effects

The safety profile of golimumab, an anti-TNF agent, is well characterised. Risks associated with treatment include serious infections including opportunistic infections, TB and Hepatite B viral reactivation, demyelinating disorders, hypertension; lymphoma and other malignancies, CHF, autoimmune processes (SLE or lupus-like syndrome), haematologic reactions, and risk for serious systemic hypersensitivity (including anaphylactic reaction). In the two studies of i.v. administration, the most commonly reported events include infections such as upper respiratory tract infections. There were also reports of serious infections, including a few cases of opportunistic infections.

Mortality in RA studies with anti-TNF agents have been assessed in depth within the PhVWP during 2010. It was concluded, that when considering the totality of data, there was no increased risk for mortality associated with anti-TNF agents used for treatment of RA. However, it was noted that the experience for golimumab was limited. The data from these two IV studies increase the experience The incidence of death per 100 subject-years in study ART3001 is somewhat higher than the incidence per 100 subject-years in study T06, 0.52 vs. 0.35 , but numbers are small, 5 deaths in study ART3001 and 4 in the T06 study. It is noted that the known causes of death in the ART3001 study point to an involvement of TNF α inhibition. The MAH should discuss the incidence difference, and provide a summary of deaths in both integrated IV studies and SC studies.

For malignancy, there is no new safety signal reported in these studies, compared with previous experience from studies with s.c. administration. Risk for malignancy is included in the PI, and the following events are included in section 4.8: *Neoplasms (such as skin cancer, squamous cell carcinoma and melanocytic naevus)* as Uncommon and *Lymphoma, leukaemia* as rare events. The RMP also adequately addresses the risk for malignancy.

Uncertainty in the knowledge about the unfavourable effects

Although the two studies of i.v. administration did not reveal any new safety concerns, when comparing to the s.c administration, this new route will result in a higher systemic exposure during the treatment interval (approx 3x for AUC and 6x for Cmax). This is due to both a higher total dose (e.g. for a 75 kg person, the total dose given i.v. during the first 12 weeks will be 450 mg, while for s.c. it will be 200 mg), and since the bioavailability after s.c. administration is lower (approx. 50% bioavailability). Based on the available safety data, it is not possible to with certainty assess whether there is a quantitative difference in the safety profile between the IV and SC route of administration or not, but a higher risk for adverse effects in the long term cannot be excluded.

The MAH provided a PK exposure/safety analysis, to explore the relationship of selected safety events to exposure. The quartile subgroups of increasing PK exposure were assessed for infections, serious

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infections and SAEs. The distribution of PK exposure versus the occurrence of these safety events as well as malignancies was also assessed. There was no clear trend of higher exposure in subjects who experienced 1 or more safety events, neither for IV nor for SC data. Since the occurrence (IV and SC combined) of serious infections and malignancies is rather low, 0.5% and 2%, respectively, firm conclusions regarding the distribution of exposure cannot be drawn. However, there is no overt difference in exposure seen comparing subjects experiencing adverse events to subjects without adverse events.

In the SC development programme, there was an apparent dose related increase in the incidence of AEs, including serious infections with the golimumab + MTX combinations (50 and 100 mg sc with MTX, respectively). The Applicant has tried to address this issue, and provided 52 weeks data on safety and efficacy from the pivotal 3001 study. Since all subjects crossed over to active drug at week 24, there is neither a placebo group nor an active treatment group for comparison. The Applicant states that the type of AEs were comparable to those observed in other studies, and makes comparisons in particular with study C0524T06, which enrolled a similar MTX non-responder subject population(subjects were administered SC golimumab 50 mg or 100 mg or placebo injections at Week 0 and every 4 weeks (q4w) thereafter through Week 48). However uncertainties regarding comparable safety remain, due to the unreliability of inter trial comparisons. Further, the relevant comparison would be safety data from ART3001 compared to safety data from SC 50mg Q4W in a similar population, whereas in study T06, 89 subjects were randomized to 50mg sc Q4W and 178 subjects were randomized to 100mg sc Q4W. After early escape at Week 16 and crossover from placebo at week 24, a total of 212 subjects received at least one dose of 50mg Q4W, whereas 237 received 100mg Q4W. A reanalysis of adverse events in 50mg SC Q4W vs. IV 2mg/kg Q8W is asked for.

In the safety data for integrated phase 3 RA IV studies, the numerical difference between placebo and golimumab-treated patients that experienced cardiac events is remarkably high, 2 vs 67 affected patients. However, figures are difficult to interpret, given that the placebo groups were smaller and the treatment period considerably shorter. The MAH is requested to provide per 100 patient years figures, from study ART 3001 and for study subjects treated with the marketed dose, as well as placebo treated subjects.

There is a tendency to more hepatic events in study ART3001 as compared to study T06, which is not alarmingly high, but may indicate a difference in the safety profile for higher exposure. This should be addressed within the requested reanalysis of the comparison of safety data.

There was a higher incidence of infusion reactions in golimumab-treated patients when combining all golimumab groups in the two IV studies. The general incidence was relatively low (2.6% subjects with at least one infusion reaction for placebo vs. 3.6% for golimumab). There were two anaphylactic reaction reported, none of which was considered to be related to golimumab. The placebo group in study ART 3001 reported significantly less infusion reactions than the placebo group in study T12. It is assumed that this is due to the fact that the placebo formulation used in study ART3001 was saline solution only and therefore did not contain any of the excipients found in the golimumab formulation. It was noted that there was a difference in the frequencies of reported adverse events in the two studies (e.g. at week 16, 43.7% and 47.3% for placebo and golimumab groups respectively in study ART3001, and 67.4% and 65.9% for placebo and golimumab groups, respectively, in study T12). However, the pattern of reported AEs was similar in the two studies. Further, for some events e.g. deaths or subjects with serious adverse events, there seemed to be the highest number in the 2 mg/kg Q12 group in T12, compared with the higher dose in the same study, or when looking at the difference between placebo and the 2 mg/kg q8 dose in study ART3001. The reasons for these observations are unclear. The MAH explained the finding with the fact that the 2 studies were performed in different geographic regions. This explanation can be accepted, but it also underlines the uncertainties adhered to between study comparisons.

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Balance

The safety profile is well established, and treatment with golimumab is connected with several potentially serious risks. However, for the currently approved SC formulation these risks can be managed with adequate information in the PI, use of a patient alert card, and via the already ongoing education programme.

The posology applied for with the new route of administration will result in a higher systemic exposure during the treatment interval both due to a higher total dose, and since the bioavailability after s.c. administration is lower (approx. 50% bioavailability). The provided data show a six fold higher Cmax for IV dosing. Considering a 70 kg patient, and a subcutaneous bioavailability of 50%, the AUC over 8 weeks following IV dosing would be approximately three times the corresponding AUC for the SC dosing of 50mg.

Regarding benefit the Applicant has provided information from 3 SC clinical trials, an observational study and two patient surveys , and the conclusion is that about a third of subjects do not wish to self inject, and that a proportion of these prefer to visit the health care office every 8 weeks instead of every 4 weeks. IV administration would thus be a more convenient alternative for these patients. However this is not a medical benefit and is considered a weak justification of a higher exposure of the drug. In drug development, the lowest effective dose is worth aiming at, and this new formulation of golimumab will exceed this, without adding to the benefit of the drug.

In the 3001 study, the rate of adverse events through 16 weeks was only marginally higher in the treated group, compared to the placebo group, however increased rates of uncommon or rare but serious side effects may not have been captured during this limited time period and limited patient population. Thus there is a potentially increased risk for unfavourable effects for the IV formulation compared to the sc formulation due to the higher systemic exposure. In the provided PK exposure/safety analysis there is no overt difference in exposure seen comparing subjects experiencing adverse events to subjects without adverse events, but firm conclusions regarding the distribution of exposure cannot be drawn.

The Applicant has provided additional safety data through week 112 in study 3001. A comparison with one of the previously conducted studies in subjects on SC golimumab, C0524T06 was made. This inter study comparison showed similar frequencies of AEs through week 52, but has the limitations of a inter study comparison, and the fact that more than half of the subjects in study T06 received twice the dose currently approved (50mg) severely hampers solid conclusions. A revised safety comparison between the proposed IV dosing and the marketed SC (50 mg) dosing is needed.

In conclusion, the higher exposure of the drug, with a Cmax that is 6 times higher and AUC which is 3 times higher than that of SC administration, raises uncertainty regarding the safety profile versus SC administration that remains for long term treatment.There is insufficient efficacy advantages identified that could outweigh this potentially increased risk. Neither is it possible to distinguish a certain patient category that would benefit from the iv formulation in terms of efficacy, and for whom the risk of increased frequency of AEs may therefore be accepted. Thus a positive B/R needs further justification (MO).

5.1. Conclusions

Further documentation is needed to support consistent production of the FVP (IV) for release to the EU market.

Given that the only benefit of IV versus SC administration of golimumab appears to be less frequent dosing, this small potential benefit is not considered outweighing the uncertainty related to safety,

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when administrating three times the dose needed to obtain the same effect. The benefit risk balance of the IV Simponi formulation is currently considered negative.

6. CHMP list of questions

6.1. Quality aspects

Major objections

None

Other concerns

Drug product

Manufacture:

1. Data should be presented from qualification of production at the proposed site.

Stability

2. Data from studies on the stability of two qualification batches should be provided.

3. The Applicant is asked to confirm that the studies on the stability of the qualification batches will be run according to the Post-Approval Stability Protocol and Stability Commitment50 mg FVP (IV) Stability Protocol - Shelf Life Extension, presented in CTD P.8.2.

4. In section P.8.2 the Company commits to continue the stability studies on the pre-process and the process validation FVP (IV) batches over the three years scheduled. As many of the drug product batches included in the studies were manufactured in 2008 and 2009, there is reason to believe that some of the studies have been finalized. The Company is therefore asked to update the reports from these studies to include currently available data.

6.2. Non clinical aspects

None

6.3. Clinical aspects

Major objections also to be addressed at a possible Oral Explanation

Major objections

Pharmacokinetics

Pharmacodynamics

Benefit / Risk balance

5. A positive benefit/risk balance for the IV formulation needs further justification. The uncertainties with respect to long term safety due to the higher exposure to golimumab after IV administration (6 times higher Cmax and a 3 times higher AUC) compared to SC administration, are not considered to be outweighed by the rather limited benefits, i.e. that IV administration of Simponi every 8 week may be a more convenient alternative for some of the patients who do not want to/cannot administer the drug themselves.

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Safety

6. In the absence of a SC 50mg Q4W arm in study ART3001, a between studies comparison was made in order to investigate any safety issues. However, the main safety concern for this product is not that there may be safety issues associated to IV administration as such, but rather that the 3 times higher systemic exposure of the drug may be associated with increased risks. Therefore the safety comparison should have been made between the currently marketed SC 50mg dose, and the proposed IV dose, as well as between the two studied SC doses (50mg and 100mg). The MAH is requested to provide this.

Other concerns

Efficacy

7. A trend towards a weakened response in antibody positive patients in ART 3001 was shown. This tendency remains at Weeks 52 and 100(ACR20 response 70.3% in subjects without antibodies 51.4% in antibody negative subjects). The overall antibody to golimumab incidences for CNTO148ART3001 at week 100 were 4.6% and 6.7% respectively. The MAH is requested to address this. Further, a discussion about the immunogenicity profile after SC and IV administration is asked for.

Safety

8. In the safety data for integrated phase 3 RA IV studies, the numerical difference between placebo and golimumab-treated patients that experienced cardiac events is remarkably high, 2 vs 67 affected patients. However, figures are difficult to interpret, given that the placebo groups were smaller and the treatment period considerably shorter. The MAH is requested to provide per 100 patient years figures, from study ART 3001 and for study subjects treated with the approved dose, as well as placebo treated subjects.

9. The incidence of death per 100 subject-years in study ART3001 is somewhat higher than the incidence per 100 subject-years in study T06, but numbers are small. It is noted that the known causes of death in the ART3001 study point to an involvement of TNF α inhibition. The MAH should discuss the incidence difference, and provide a summary of deaths in both integrated IV studies and from the SC studies; presented by dose as well as by administration route.

10. More AEs were seen in patients who switched from SC to IV than in those who did not. This should be discussed by the MAH, and AE/SAE incidences per PTY for the different arms should be presented, and a wording for the PI proposed.

Risk management plan

11. The MAH is requested to provide an updated RMP that has been merged with the latest updated RMP, and where long term safety on use of IV formulation is added to missing information.

Pharmacovigilance system

The summary of the pharmacovigilance system should be provided in module 1.8.1 of the application and includes the following elements:

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- proof that the applicant has at its disposal a qualified person responsible for pharmacovigilance;
- the Member States in which the qualified person resides and carries out his or her tasks;
- the contact details of the qualified person;
- a statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in title IX of Directive 2001/83/EC;
- a reference to the location where the pharmacovigilance-system master file (PSMF) for the medicinal product is kept.

The applicant may combine this information in one single statement using the required statement as per Article 8(3)(ia): 'the applicant has the necessary means to fulfil the tasks and responsibilities listed in title IX of Directive 2001/83/EC, signed by the applicant and qualified person for pharmacovigilance (QPPV).'

If available, the PSMF number (MFL EVCODE) assigned by the extended EudraVigilance Medicinal Product Dictionary (XEVMPD) should be included in the statement in module 1.8.1

6.4. New active substance status

N/A

7. Recommended conditions for marketing authorisation and product information

7.1. Conditions for the marketing authorisation

The same conditions as for the s.c. product should apply.

7.2. Summary of product characteristics (SmPC)

No comments on the PI are made at this stage, given the negative B/R balance.

7.3. Labelling

See 7.2

7.4. Package leaflet (PL)

See 7.2

User consultation

The applicant has proposed a bridging to a user test carried out on the package leaflet (PL) of the approved subcutaneous presentation of Simponi 50 mg solution for injection in a pre-filled syringe. The user test of the mother leaflet was assessed and accepted in the procedure approved on 1st October 2009. A package leaflet for Simponi 50 mg solution for injection in a pre-filled pen was also approved in parallel to the pre-filled syringe, and a bridging of PL was accepted. The applied product is intended for intravenous use.

According to the applicant, the design and layout of the PL for the applied Simponi will match the existing PL for subcutaneous Simponis design and layout and will be developed according to the applicable EU guidelines, also no changes that may affect its readability are expected.

In order for a bridging to be formally acceptable, the applicant should have fulfilled a number of points, including procedure number in which the mother PL has been accepted. The discrepancy between the package leaflet for the applied product and the mother leaflet should have been presented in more detail e.g. in a table by the applicant. Every discrepancy between the PLs should have been justified

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why it is as good or even better in the matter of legibility. However, the assessor considers this bridging acceptable.