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SCIENCE MEDICINES HEALTH

22 April 2021
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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Onureg

International non-proprietary name: azacitidine

Procedure No. EMEA/H/C/004761/0000

Note

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

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CELGENE 2142
APOTEX v. CELGENE
IPR2023-00512

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List of abbreviations

Abbreviation or Specialist Term	Explanation
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the curve
AUCss	Area under the concentration curve at steady state
BMI	Body mass index
BSC	Best supportive care
CCR	Conventional care regimens
CHMP	Committee for Human Medicinal Products
CI	Confidence interval
Clcr	Creatinine clearance
Cmax	Maximum concentration
Cmax,ss	Peak plasma concentration at steady state
CMML	Chronic myelomonocytic leukemia
CR	Complete remission
CRF	Case report form
CRi	Complete remission with incomplete blood count recovery
CSR	Clinical study report
CYP	Cytochrome P450
DFS	Disease-free survival
DNA	Deoxyribonucleic acid
DS	Differentiation syndrome
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area
EFS	Event-free survival
ELN	European LeukemiaNet
EMA	European Medicines Agency
EP	Eosinophilic pneumonia
EQ-5D-3L	European Quality of Life-Five Dimensions-Three Levels
ER	Exposure-response
EU	European Union
EU-27	European Union of 27 member states
FAB	French-American-British (classification system)
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue
FDA	Food and Drug Administration
FLT3	fms-like tyrosine kinase 3
G-CSF	Granulocyte colony-stimulating factor
GCP	Good Clinical Practice
GO	Gemtuzumab ozogamicin
HDC	Histamine dihydrochloride
HMA	Hypomethylating agent
HR	Hazard ratio
HRQoL	Health-related Quality-of-Life
HSCT	Hematopoietic stem cell transplantation
ICF	Intended commercial formulation
ICH	International Council for Harmonisation
IDH	Isocitrate dehydrogenase

IPSS	International Prognostic Scoring System
ISS	Integrated Summary of Safety
ITD	Internal tandem duplication
ITT	Intent-to-treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWG	International Working Group
KIR	Killer-cell immunoglobulin-like receptor
LDAC	Low dose-cytarabine
LFS	Leukemia-free survival
MA	Marketing authorisation
MDS	Myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Affairs
MID	Minimally important difference
mITT	Modified intent-to-treat
MM	Multiple myeloma
MRD	Minimal residual disease
NCCN	National Comprehensive Cancer Network
NDA	New Drug Application
OS	Overall survival
PD	Pharmacodynamic
PK	Pharmacokinetics
PML	Progressive multifocal leukoencephalopathy
PT	Preferred term
QD	Once daily
RA	Refractory anaemia
RAEB	Refractory anaemia with excess blasts
RAEB-T	Refractory anaemia with excess blasts in transformation
RARS	Refractory anaemia with ringed sideroblasts
RBC	Red blood cell
RFS	Relapse-free survival
RNA	Ribonucleic acid
SAP	Statistical Analysis Plan
SBP	Summary of Biopharmaceutical Studies
SC	Subcutaneous
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SMQ	Standard MedDRA query
SOC	System organ class
SPA	Special Protocol Assessment
TEAE	Treatment-emergent adverse event
UK	United Kingdom
US	United States
WBC	White blood cell
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Celgene Europe Limited submitted on 30 April 2020 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Onureg, through the centralised procedure. As this application concerns active substance(s) already authorised via the centralised procedure, 'automatic' access was granted by the CHMP on 26 March 2020.

During the procedure, the applicant was changed to Bristol-Myers Squibb Pharma EEIG.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

New active substance status

The applicant indicated the active substance azacitidine contained in the above medicinal product to be considered as a known active substance.

Scientific advice

The applicant received the following Scientific Advice from the CHMP on the Quality development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
31 January 2019	EMEA/H/SA/4006/1/2018/I	Ms Audrey Sultana, Prof. Dieter Deforce

The Scientific Advice pertained to the following quality aspects:

- Adequacy of the data presented to support the proposed batch size for commercial production of the intended commercial formulation.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: John Joseph Borg Co-Rapporteur: Fátima Ventura

The application was received by the EMA on	30 April 2020
The procedure started on	21 May 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	10 August 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	10 August 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	18 August 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	17 September 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	21 December 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	01 February 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 February 2021
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	25 February 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	22 March 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	07 April 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Onureg on	22 April 2021
The CHMP adopted a report on similarity of Onureg with Dacogen, Rydapt, Mylotarg, Vyxeos liposomal, Xospata and Daurismo on (Appendix 1)	22 April 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Onureg was proposed to be indicated as maintenance therapy in adult patients with acute myeloid leukaemia (AML) who achieved complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following induction therapy with or without consolidation treatment and who are not candidates for, including those who choose not to proceed to, hematopoietic stem cell transplantation (HSCT).

2.1.2. Epidemiology

In the EU, the occurrence of newly diagnosed AML was estimated at approximately 18,000 cases annually (Rodriguez-Abreu, 2007) with age-adjusted incidence of 3.7 per 100,000 annually (4.0 per 100,000 for males and 3.4 per 100,000 for females) (Visser, 2012). Based on the incidence data and the total European Union of 27 member states (EU-27) population, 42,795 new diagnoses of myeloid malignancies occur in the EU-27 annually, including 18,376 cases of AML (43%). The complete AML prevalence proportion as of 01 Jan 2003 was 11.0 per 100,000 persons with an estimated 54,619 cases in the EU-27 in 2008. Based on this, the estimated prevalence of AML in Europe is approximately 1.1 per 10,000 persons (Visser, 2012). In the US, it is estimated that 21,430 new AML cases and 10,920 deaths would have occurred in 2019 (Siegel, 2019). The age-adjusted incidence of AML in the US is 4.3 per 100,000 annually in the US (Shallis, 2019). Overall, the incidence of AML increases with age with median age at diagnosis of 68 years and median age at death of 72 years and the age adjusted incidence for those older than 65 years being 20.1 per 100,000 person-years compared with 2.0 per 100,000 person-years for individuals younger than 65 (Visser, 2012; SEER cancer statistics review, 1975-2015; Shallis, 2019). The proportion of males:females diagnosed with AML is 1.6:1 with an age-adjusted incidence of 5.42 and 3.47 per 100,000 person-years, respectively (Shallis, 2019).

In Europe, the annual incidence of AML in adults is 5 to 8 cases per 100.000 individuals with a mortality rate of 4 to 6 cases per 100.000. (1) The median age at diagnosis is 67 years, but the incidence increases by age with a projected incidence of 15 to 25 cases per 100.000 in patients who are 70 years of age or older.

2.1.3. Biologic features, Aetiology and pathogenesis

AML is a rare, heterogeneous, and aggressive hematologic malignancy characterized by rapid progression of the disease and symptoms and is uniformly fatal if not treated.

Acute myeloid leukaemia is a form of leukaemia, characterised by infiltration of proliferative, clonal, abnormally differentiated, and occasionally poorly differentiated haematopoietic cells of myeloid lineage in the bone marrow, blood, and other tissues.

Factors that influence prognosis in AML include both patient-related factors and disease-related factors, with age at diagnosis being the most significant patient-related factor and genetic risk category being the most influential disease-related factor (Döhner, 2017; Shallis, 2019).

Cytogenetic and molecular genetic risk categorization are major prognostic factors for determining relapse and OS outcomes and form the basis for the European LeukemiaNet (ELN) genetic risk stratification (Döhner, 2017; NCCN-AML, 2019). Likewise, the presence of complex or monosomal karyotypes in AML is an important prognostic factor associated with extremely poor prognosis (Döhner, 2017; NCCN-AML, 2019).

The risk stratification criteria outlined by the ELN are used to determine which patients should be considered for allogeneic HSCT. In general, patients with favorable risk receive postinduction consolidation therapy and are generally not referred for transplantation unless there is evidence of conventional chemotherapy failure. In contrast, patients with adverse risk are known to have poor outcome despite intensive chemotherapy and are generally referred for HSCT if remission is achieved, a suitable donor is available, and the patient does not have serious comorbidities. The incidence of adverse genetics increases with age, so that they are frequently encountered in older patients who more often have comorbidities and poor performance status, and thus are not candidates for intensive remission induction therapy and HSCT. Therefore, prognosis for AML is generally inferior for older patients, resulting in less discriminatory relevance of molecular risk markers (Döhner, 2017).

Minimal residual disease (MRD) is an important prognostic factor to monitor after diagnosis and following remission as the presence of MRD identifies patients at high risk of disease recurrence and short survival. The ELN recommendations include a proposal for a response category based on MRD status since despite morphologic remission, patients frequently have evidence of persisting MRD as assessed by flow cytometric (multiparameter flow cytometry [MFC]) or quantitative molecular methods that include real-time quantitative PCR (RT-qPCR), digital PCR, and next-generation sequencing-based technologies. Minimal residual disease can be assessed at early time points, for example, following induction and consolidation to assess remission status and determine kinetics of disease response, and sequentially beyond consolidation to detect impending morphologic relapse. (Döhner, 2017).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

AML is a heterogeneous disease; the classification is based on morphologic, cytogenetic, molecular, and immunophenotypic features, which, along with baseline patient characteristics such as age and performance status (PS), influence outcome and treatment recommendations (4). Among these, baseline cytogenetic risk constitutes one of the most significant prognostic markers of disease outcome (5). Age is the most prominent patient-specific risk factor, and cytogenetics the most disease-specific risk factor.

In AML, leukaemic blasts replace normal blood cells in bone marrow and peripheral blood, which leads to anaemia, neutropenia, and thrombocytopenia. This is associated with symptoms of fatigue, shortness of breath, disturbed wound healing, infections and bleedings. If left untreated, AML results in death within a few weeks to months.

Long-term survival in adult patients with AML is only 35% to 40% for patients ≤60 years of age, and drops to 5% to 15% in patients who are >60 years of age. (6) The majority of patients with AML will have relapsed disease within 3 years.

2.1.5. Management

The usual treatments for newly diagnosed AML patients without serious comorbidities include intensive chemotherapy to induce remission (induction chemotherapy). Intensive induction chemotherapy typically consists of cytarabine in combination with an anthracycline. In order to deepen the level of remission through

eradication of residual leukemia, patients typically receive consolidation chemotherapy. There is no consensus regarding the optimal approach to the number of cycles of consolidation therapy.

The therapeutic approaches for patients who can tolerate intensive therapy are usually divided into two phases: induction of remission and post-remission (consolidation) therapy. Although patients can achieve CR and disease control after induction, patients who do not receive post remission consolidation therapy are more likely to relapse, usually within 6 to 9 months. Post remission therapy is recommended for patients younger than 60 years old and for older patients who are fit for intensive therapy.

For patients who cannot tolerate intensive induction therapy, combinations of low intensity therapy with novel agents such as venetoclax and glasdegib has shown improved responses and/or survival.

Allogeneic HSCT is the only potentially curative treatment for patients with AML. However, HSCT is not a feasible treatment option for many patients, and the frequency of patients undergoing HSCT decreases with increasing age due to the increased prevalence of comorbidities and poor organ function limiting the benefit-risk assessment of the procedure. Despite treatment with consolidation chemotherapy, and even HSCT, relapse rates after these therapies remain high and contribute to the poor outcomes in AML. Salvage therapy following relapse is limited, particularly for patients who are not candidates for transplant. Intensive chemotherapy can offer the highest CR rates; however, its application is limited by tolerability, in particular, the high treatment-related mortality and short remission duration.

Maintenance therapy conducive to long-term tolerable drug administration could potentially prolong remission and survival in the post-consolidation setting, particularly in those with intermediate risk and high-risk disease as well as those who do not proceed to transplant. Despite the approval of several maintenance therapies for AML, given the lack of convincing benefit, maintenance therapy with these agents is globally not considered standard of care. Effective maintenance therapy could provide an important therapeutic approach to treatment of patients with AML, a disease associated with short survival and a high unmet medical need.

Current salvage therapy at time of relapse is inadequate, particularly for subjects not eligible for transplant. Duration of first Complete Remission (CR) is an important predictor of outcome, with longer duration of first CR associated with better survival. Therefore, maintaining patients in CR is an important therapeutic goal in AML. As most patients will relapse, effective maintenance treatment for patients who do attain remission may play a role in preventing relapse and prolonging OS, especially in those for whom HSCT is not feasible.

Maintenance Therapies Approved in the European Union:

- Rydapt (midostaurin) was approved in the EU in 2017 as maintenance therapy for newly diagnosed patients with AML with FLT3 mutation, in first remission following midostaurin in combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy, based on a Phase 3 trial (RATIFY; Stone, 2017). In this study, 717 newly diagnosed patients with FLT3 mutant AML aged 18 to 59 years old, were randomized to receive standard chemotherapy (induction and consolidation) in combination with either the FLT3 inhibitor midostaurin (N = 360) or placebo (N = 357). Patients who achieved remission after consolidation therapy entered the maintenance phase and received midostaurin (N = 120) or placebo (N = 85) for an additional 12 months. The primary endpoint was OS, measured from time of randomization to death. Both OS and event-free survival (EFS) were significantly longer in patients treated with midostaurin compared with placebo (hazard ratio [HR] = 0.78; p = 0.009 for OS and 0.002 for EFS). Although there was a significant increase in OS, the specific contribution of maintenance midostaurin is not certain, as the maintenance portion of the study was neither randomized nor powered to determine the effect of midostaurin in maintenance setting. Additionally, the inclusion of midostaurin with induction treatment prior to maintenance, did not allow for determination of the independent effect of maintenance therapy. And lastly, midostaurin is targeted against

FLT3 mutant AML and therefore, it's use is limited to this patient population, which comprises 30% of AML cases (Kindler, 2010).

- Ceplene (histamine dihydrochloride [HDC]), in combination with IL-2, was approved in the EU/EEA in 2010 as maintenance therapy for adult patients with AML in first remission based on an open label randomized Phase 3 study (Brune, 2006). The study enrolled patients ≥ 18 years old with de novo or secondary AML with verified CR following induction and consolidation chemotherapy. A total of 320 patients were enrolled; 261 patients in first remission and 59 patients in subsequent remission. Patients were randomized 1:1 to receive either HDC/IL-2 for 10 consecutive 3-week cycles or no treatment (control) for a total of 18 months or until relapse/discontinuation. Median age was 55 years old (18 to 81) and 54 years old (18 to 84) in the HDC/IL-2 and control arms, respectively. The primary efficacy endpoint was duration of leukemia-free survival (LFS). The study demonstrated significant improvement in LFS (HR = 0.71; p = 0.01) particularly in the subgroup of patients in first CR (HR = 0.69; p = 0.01) but not for patients in subsequent CR (HR = 0.79; p = 0.4); however, OS was not significantly improved neither in the overall population (p = 0.2) nor in the subgroups of patients in first or subsequent CR (p = 0.2 and > 0.5, respectively). The results of this study may have been confounded by the fact that 18% of patients enrolled were beyond first remission and 21% were enrolled > 6 months after achieving CR. Also, the study was not powered for differences in OS. In addition, the efficacy of HDC/IL-2 as maintenance in patients older than 60 years old has not been fully demonstrated.

In summary, while both treatments have been approved in the maintenance setting in the EU, Rydapt and Ceplene have not been adopted by ELN for use in AML. This is due to limitations in the data as well as challenges to the use of the agents (e.g., patient population, study design limitations and side effects).

The injectable form of azacitidine – Vidaza (azacitidine), is approved in the European Union (EU) for the treatment of adult patients who are not eligible for hematopoietic stem cell transplant (HSCT) with:

- intermediate-2 and high-risk MDS according to the International Prognostic Scoring System (IPSS),
- chronic myelomonocytic leukaemia (CMML) with 10-29% marrow blasts without myeloproliferative disorder,
- Acute myeloid leukemia (AML) with 20-30% blasts and multi-lineage dysplasia, according to WHO classification,
- AML with >30% marrow blasts according to the World Health Organization (WHO) classification.

About the product

Onureg is an oral formulation of azacitidine. Azacitidine is a DNA methyltransferase inhibitor and epigenetic modifier.

Azacitidine is incorporated into DNA and RNA following cellular uptake and enzymatic biotransformation to nucleotide triphosphates. Incorporation of azacitidine into the DNA of cancer cells, including acute myeloid leukemia cells, modified epigenetic pathways through the inhibition of DNA methyltransferases, reduction of DNA methylation, and alteration of gene expression, including re-expression of genes regulating tumor suppression, immune pathways, cell cycle, and cell differentiation.

Incorporation of azacitidine into the RNA of cancer cells, including leukemic cells, inhibited RNA methyltransferase, reduced RNA methylation, decreased RNA stability, and decreased protein synthesis. Anti-leukemic activity of azacitidine was demonstrated by reduction of cell viability and induction of apoptosis in

acute myelogenous leukemia (AML) cell lines in vitro. In vivo, azacitidine decreased tumor burden and increased survival in leukemic tumor models.

Pharmacotherapeutic group: Antineoplastic agents, Antimetabolites, Pyrimidine analogues

Onureg is indicated as maintenance therapy in adult patients with acute myelogenous leukemia (AML) who achieved complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following induction therapy with or without consolidation treatment, and who are not candidates, including those who choose not to proceed to, hematopoietic stem cell transplantation (HSCT).

The proposed starting dose is 300 mg orally, once daily (QD) for the first 14 days of each 28-day cycle.

In the case of disease relapse during therapy with 5% to 15% blasts in peripheral blood or bone marrow, in conjunction with clinical assessment, the dosing schedule indicates that it may be extended from 14 days to 21 days of repeated 28-day cycles.

Type of Application and aspects on development

This submission is a complete and independent application.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 200 or 300 mg of azacitidine.

Other ingredients of the tablet core are: croscarmellose sodium (E468), magnesium stearate (E570), mannitol (E421) and silicified microcrystalline cellulose (E460, E551). Film coating of 200 mg tablets consists of Opadry II pink containing: hypromellose (E464), titanium dioxide (E171), lactose monohydrate, polyethylene glycol/macrogols (E1521), triacetin (E1518) and iron oxide red (E172). Film coating of 300 mg tablets consists of Opadry II brown containing: hypromellose (E464), titanium dioxide (E171), lactose monohydrate, polyethylene glycol/macrogols (E1521), triacetin (E1518), iron oxide red (E172), iron oxide yellow (E172) and iron oxide black (E172).

The product is available in nylon (OPA) / polyvinyl chloride (PVC) aluminium blisters with push through aluminium foil as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of azacitidine is (2*R*,3*R*,4*S*,5*R*)-4-amino-1-(3,4-dihydroxy-5-hydroxymethyl-tetrahydro-furan-yl)-1*H*-[1,3,5]triazin-2-one corresponding to the molecular formula $C_8H_{12}N_4O_5$. It has a molecular mass of 244.207 g/mol and the following structure:

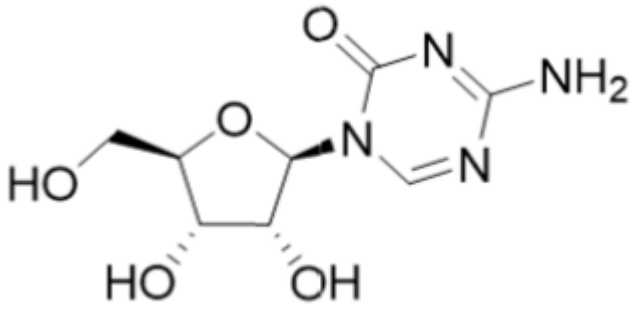


Figure 1: active substance structure

The chemical structure of azacitidine was elucidated by a combination of elemental analysis, mass spectrometry, NMR spectroscopy, FTIR spectroscopy, UV spectroscopy. The solid state properties of the active substance were measured by single crystal X-ray analysis, X-ray powder diffraction, differential scanning calorimetry and thermo-gravimetric analysis.

The active substance is a white to off-white solid, it is non-hygroscopic and highly soluble in aqueous media across a wide range of pH.

Azacitidine exhibits stereoisomerism due to the presence of four chiral centres. The chirality of azacitidine originates from the ribose moiety of the molecule. Enantiomeric purity of D-ribose starting material is controlled during its synthesis.

Polymorphism has been observed for azacitidine. Nine different solid forms of azacitidine were identified, including eight crystalline forms and one amorphous form. Form I was determined to be the thermodynamically most stable form at ambient conditions. The validated active substance manufacturing process has consistently produced azacitidine Form I as the used solvent system (2-propanol/DMSO) generated pure Form I only, and no other polymorphs were generated during polymorph studies in this solvent system. Polymorphic form is routinely tested during active substance release. The solid form of the active substance remained unchanged during finished product manufacturing process. In addition, no form conversion was observed in tablet stability samples.

The full information on the active substance was provided in the submitted dossier. Azacitidine is a known active substance, included in the centrally authorised medicinal product Vidaza (azacitidine 25 mg/mL powder for suspension for injection). In respect to manufacture of azacitidine, it is declared by the applicant that the information is the same as for currently authorised Vidaza MA except for the inclusion of an additional testing site for the active substance for physical properties (XRPD and PSD) and the reference to manufacturing site for starting materials.

Manufacture, characterisation and process controls

Azacitidine is manufactured by two suppliers who use an identical manufacturing process and it is synthesized in a convergent synthesis in seven chemical transformation and a purification step using well-defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

Three processes for the manufacture of azacitidine have been used during clinical development in producing both pilot scale and production-scale batches. These processes are designated as Processes A, B, and C. Manufacturing Process C is the commercial active substance manufacturing process. All three processes use the following sequence of reactions. Changes introduced have been presented in sufficient detail and have been justified.

The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged in polyethylene bags which comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for: appearance, colour, identification (FT-IR, HPLC), solid form (XRPD), assay (HPLC), related substances (HPLC), optical rotation (Ph. Eur.), residual solvents (GC), residue on ignition (Ph. Eur.), bacterial endotoxins (LAL), particle size distribution (Ph. Eur.), water content (KF) and microbial limits (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on 1 pilot and 19 commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from two pilot scale an three commercial scale batches of active substance from the manufacturer used during the development only stored in the intended commercial package for up to 48 months under long term conditions (5°C ± 3°C) and for up to 6 months under accelerated conditions (25°C / 60% RH) according to the ICH guidelines were provided.

Stability data from eleven commercial scale batches of active substance from the proposed commercial manufacturer stored in the intended commercial package for up to 36 months under long term conditions (5°C ± 3°C) according to the ICH guidelines were provided in addition.

Stability data from four commercial scale batches of active substance from the second proposed commercial manufacturer stored in the intended commercial package for up to 36 months under long term conditions (5°C ± 3°C) and for up to 6 months under accelerated conditions (25°C / 60% RH) according to the ICH guidelines were also provided.

The following parameters were tested: description, water content, microbial limits, assay and related substances. The analytical methods used were the same as for release and were stability indicating. All tested parameters were within the specifications.

Photostability testing following the ICH guideline Q1B was performed on one batch, showing that azacitidine is not photosensitive.

Results on stress conditions (thermal, light, oxidation, acid, and base) were also provided on one batch. It was shown that azacitidine is sensitive to thermal and oxidative stress and acid and base hydrolysis, but it is stable under light exposure.

An evaluation of polymorphic stability was performed on three active substance batches up to 48 months under long-term storage conditions and up to 6 months under accelerated storage conditions. The data demonstrate that no changes in polymorphic form were observed under any of the conditions studied for the duration of the evaluation.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is presented as a solid oral immediate release dosage form - film-coated tablets containing either 200 or 300 mg of azacitidine. Onureg 200 mg film-coated tablets are pink, 17.0 x 7.6 mm in size, debossed with "200" on one side and "ONU" on the other side. Onureg 300 mg film-coated tablets are brown, oval, 19.0 x 9.0 mm in size, debossed with "300" on one side and "ONU" on the other side. The two strengths differ in size, colour and debossing.

Pharmaceutical development of the finished product contains QbD elements.

The quality target product profile (QTPP) is presented.

The formulation and manufacturing development have been evaluated through the use of risk assessment to identify the critical product quality attributes and critical process parameters. A risk analysis was performed using the failure mode effect analysis (FMEA) method in order to define critical process steps and process parameters that may have an influence on the finished product quality attributes. The risk identification was based on the prior knowledge of products with similar formulations and manufacturing processes as well as on the experience from formulation development, process design and scale-up studies. The critical process parameters have been adequately identified.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Azacitidine is shown to be compatible with excipients based on excipient compatibility studies and stability data for the intended commercial formulation.

The primary packaging is nylon (OPA) / polyvinyl chloride (PVC) aluminium blisters with push through aluminium foil. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of four main steps: dry blending, tablet compression, film coating and packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. The validation consisted of three consecutive batches of 200 mg dosage strength and four consecutive batches of 300 mg dosage strength utilizing the proposed commercial process and scale and using active substance provided by both manufacturers. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs. Design space and regulatory flexibility has not been claimed.

Product specification

The finished product release specifications shown in Table 7 include appropriate tests for this kind of dosage form: appearance, identification (HPLC-UV, UV), assay (HPLC-UV), uniformity of dosage units (HPLC), degradation products (HPLC-UV), dissolution (Ph. Eur., HPLC), water content (Ph. Eur.) and microbial limits (Ph. Eur.).

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided on six commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 4 commercial scale batches per strength of finished product (3 manufactured by the first active substance supplier and 1 by the second) stored for up to 24 months under long term conditions (25°C / 60% RH) and for up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. The batches of the medicinal product are identical to those proposed for marketing and were packed in the primary packaging representative of the one proposed for marketing.

Samples were tested for appearance, assay, degradation products, dissolution and microbial limits. The analytical procedures used are stability indicating. Neither significant changes nor trends have been observed.

Stressed studies were conducted for the finished product under acidic, basic, oxidative, thermal/humidity, and light conditions. Under all conditions, the finished product assay and degradation product methods achieved adequate resolution of all degradation peaks. Acceptable mass balance was obtained for all conditions evaluated. The finished product assay and degradation product methods are considered stability-indicating.

In addition, one batch per strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No degradation products were detected in the finished product in the intended commercial package. Based on these results, the finished product is not light sensitive.

Based on available stability data, the proposed shelf-life of 36 months as stated in the SmPC (section 6.3) are acceptable. This medicinal product does not require any special storage conditions.

Adventitious agents

No excipients derived from animal or human origin have been used. Magnesium stearate is vegetable derived.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the active substance and/or finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

The risk assessment on presence of nitrosamine impurities has been conducted and no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical data submitted in this MAA application are based on applicant-sponsored studies, bibliographical information, and NCI-sponsored studies. Most of the non-clinical studies were conducted in the 1960s and 1970s before the introduction of Good Laboratory Practice (GLP) regulations and International Conference on Harmonisation (ICH) guidelines.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Most of the primary pharmacodynamics studies presented in this application derive from data published in the literature, some of them since many decades.

Experimental evidence suggests that azacitidine acts through several mechanisms of action, among which demethylation of DNA and cytotoxicity appear to be the prevailing ones. Anti-leukemic activity of azacitidine was demonstrated by reduction of cell viability and induction of apoptosis in AML cell lines *in vitro*.

Azacitidine is a pyrimidine nucleoside analog of cytidine that inhibits DNA/RNA methyltransferases. Azacitidine is incorporated into DNA and RNA following cellular uptake and enzymatic biotransformation to nucleotide triphosphates. The primary pharmacodynamic effects are inhibition of DNA methyltransferases, reduction of DNA methylation and induction of cytotoxicity. Incorporation of azacitidine into the RNA of cancer cells, including leukemic cells, inhibits RNA methyltransferases, reduces RNA methylation, decreases RNA stability and decreases protein synthesis. In populations of proliferating cells, each generation of cells is expected to have less 5-methycytosine leading to expression of genes previously suppressed by hypermethylation. Hypermethylation of tumor suppression genes has been correlated with several leukemias and solid tumors in humans. The capacity of azacitidine to inhibit DNA methylation in tumor cells is expected to cause these cells to progress to their normal differentiated phenotype. The doses of azacitidine required to inhibit DNA methylation are generally several fold less than the maximum doses previously used to treat AML.

The applicant included reports investigating the *in vivo* pharmacology of azacitidine delivered by intraperitoneal injection. *In vivo*, azacitidine decreased tumor burden and increased survival in leukemic tumor models.

In this frame, the applicant has justified how these data can be interpreted with respect to the intended oral formulation since differences between routes of administration have not introduced any significant variability or bias in the results of the non-clinical pharmacology studies.

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies were submitted.

Azacitidine can have immunosuppressive and antimicrobial effects (Hanka, 1966; Paluska, 1982; Vadlamudi, 1970). It is acknowledged that these secondary effects are similar to those associated with other nucleoside analogues used as antiviral and antineoplastic agents.

Safety pharmacology programme

The applicant has provided non-clinical GLP-compliant *in vivo* safety pharmacology studies testing IV azacitidine on central nervous system, respiratory and cardiovascular systems. In single dose safety pharmacology studies in rats, azacitidine produced different central nervous system (CNS)-related clinical signs and altered several respiratory functional parameters at a dose that was comparable to the lethal dose in 10% of the rats (LD10). Thus, azacitidine-related effects on CNS and respiratory parameters were attributed to its toxicity.

An *in vivo* safety pharmacology study in dogs receiving azacitidine reported increased QTc interval, but interpretation of this study is limited by confounding effects associated with systemic toxicities of azacitidine.

Follow-up non-clinical studies have been conducted and include in vitro studies to assess the vasodilatory potential in the isolated rat aorta, potential for chronotropic effects in the isolated guinea pig atria, and effects on heart rate and contractility in isolated perfused guinea pig hearts. In these studies, no direct effects of azacitidine were observed on vasodilatory parameters on the isolated rat aorta, no positive chronotropic effect was observed on the pacemaker activity of the guinea pig right atria, although a weak negative chronotropic effect was seen at the highest concentration, and there was no effect on heart rate and contractility in the isolated perfused guinea pig hearts.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were submitted.

2.3.3. Pharmacokinetics

In animals, azacitidine was rapidly absorbed in mouse, rat, and dog following SC or PO administration. Azacitidine presents poor PO bioavailability in the range of (22-38%) in the rats, mice and dog. There were no consistent gender differences observed following PO administration. Following multiple PO doses, no accumulation was observed, which was consistent with the short t1/2 (< 1 hour) of azacitidine.

Studies showed that azacitidine has a wide tissue distribution following SC or IV administration to rats, and IV or PO administration to mice. Other than the excretion/metabolic and gastrointestinal system, relatively higher azacitidine-related radioactivity was present in spleen, bone marrow and thymus. The radioactivity in tissues declined steadily over time. Azacitidine penetrates also into CSF and brain following IV or PO administration to rats. Plasma protein binding of azacitidine suggests that the in vitro protein binding of azacitidine in human serum is low.

Azacitidine is not metabolized by cytochrome P450 isozymes (CYPs). Metabolism of azacitidine is by spontaneous hydrolysis and by deamination mediated by cytidine deaminase (CDA). In vitro and in vivo studies have demonstrated that while there were some quantitative differences, spontaneous hydrolysis of azacitidine is the major pathway in different species, regardless of the route of administration. Although quantitative differences have been observed, no qualitative difference in metabolite profiles have been observed among species. CDA is the primary pathway for the breakdown of azacitidine to the less active, 5-azauridine. Levels

of cytidine deaminase activity in blood varies greatly among mammalian species and this may explain the greater sensitivity of dogs and rodents to azacitidine compared to humans. Although a limited number of case reports correlated CDA polymorphisms to changes in the clinical outcome of azacitidine therapy, this evidence remains limited and do not constitute a definite proof that pharmacogenomics can significantly impact on the efficacy and safety of azacitidine.

Urine was the major excretion route of radioactivity in mice and rats following PO, SC or IV dose of ^{14}C-azacitidine. Similar excretion profiles were observed with the IV and SC administration to rats. The parent drug accounted for a small portion of urinary radioactivity (approximately ≤ 5%).

In vitro, azacitidine was not an inducer or inhibitor of CYPs at clinically achievable plasma concentrations. Hence, azacitidine will not produce clinically relevant PK drug-drug interactions due to CYP enzyme inhibition or induction when co-administered with CYP substrates, inducers, or inhibitors.

Azacitidine was not a substrate for P-glycoprotein (P-gp). At 50 µM, azacitidine had no notable inhibitory effect on the transport of digoxin. CC-486 was not an inhibitor of breast cancer resistance protein (BCRP), organic anion transporters (OAT) OAT1 and OAT3, organic anion transporting polypeptides (OATP) OATP1B1 and OATP1B3, or organic cation transporter (OCT) OCT2. Therefore, azacitidine is unlikely to produce any clinically relevant interactions with substrates of these transporters, or an inhibitor or inducer of P-gp.

Uptake of azacitidine was mediated by all 7 human nucleoside transporters (hCNT1, hCNT2, hCNT3, hENT1, hENT2, hENT3, and hENT4) tested, with hCNT3 showing the highest activity.

2.3.4. Toxicology

Single dose toxicity

The applicant presented single dose toxicity studies conducted in rodents in 1970s and early 1980s according to the guidelines and standards of that period (non-GLP compliant). Single-dose studies were conducted in mice, rats, and dogs using PO, IP, and IV routes of administration.

The main findings are summarized in the following Table 8:

Table 1: Single dose toxicity studies (azacitidine)

Study ID	Species/ Number per sex and group	Dose (mg/kg)/Route	Approx. lethal dose / observed max non-lethal dose (mg/kg)	Major findings
PH-43-65-61 *(Palm 1970)*	Swiss mice / 10	0, 431, 519, 624, 750 / oral (gavage)	LD_{10} 455 LD_{50} 572 LD_{90} 750/ < 431	> 431: ↓ weight gain > 519: ↓ liver glycog. Toxicity in males > females Mean time of death was day 4

Study ID	Species/ Number per sex and group	Dose (mg/kg)/Route	Approx. lethal dose / observed max non-lethal dose (mg/kg)	Major findings
PH-43-65-61 *(Palm 1970)*	Swiss mice / 10	0, 79.2, 99.7, 125.6, 158.1 / i.p.	LD_{10} 89 LD_{50} 116 LD_{90} 146 / 79.2	≥ 99.7: ↓ weight gain Degeneration of kidney tubules and hepatocytes Toxicity in males > females Mean time of death was day 4
ADL-NCI 73-43 *(Palm 1973)*	Swiss mice/ 10	0, 62.9, 79.2, 99.7, 125.6, 158.1/ i.v. (PVP formulation)	LD_{10} 87 LD_{50} 117 LD_{90} 172 / 79.2	≥79.2: ↓ weight gain ≥62.9: extramedullary hematopoiesis (spleen) Mean time of death was day 6
6133-100 *Reno 1983 (US GLP)*	$CD2F_1$ mice/ 10	0, 150, 173, 199, 229, 264, 304, 350/ i.v. (Lactated Ringer's)	LD_{10} 199 LD_{50} 250 LD_{90} 313 / 150	≥173 ↓ weight gain ♀ ≥264 ↓ weight gain ♂ Deaths occurred days 3-11
ADL-NCI 73-43 *(Palm 1973)*	SD rats/ 10	0, 41, 46.1, 51.7, 58, 65.1/ i.v. (PVP formulation)	LD_{10} ≈38.5 LD_{50} 51.4 LD_{90} ≈64.5 / 41	≥46.1: ↓ weight gain ≥51.7: ↑ hepatic lipid 92% of deaths occurred by day 6
Palm 1970 PH-43-65-61	Beagle dogs/ One animal per dose (2F+1M)	3.32, 6.65, 13.2/ i.v.	13.2 / 6.65	≥3.32: ↓ WBC, ↑ SGPT 13.2: moribund, sacrifice on day 2 Severe weight loss ↑ BUN. SGOT, SGPT Degenerative changes in bone marrow, lymphatic tissues, kidney, and liver

Repeat dose toxicity

The applicant presented repeat dose toxicity studies conducted in 1970s and early 1980s according to the guidelines and standards of that period (non-GLP compliant). Repeat-dose toxicity studies have been carried out in mice (oral, i.p., and i.v.), dogs (i.v.), and monkeys (i.v.), as summarised in the following Table 9.

Table 2:

Study ID	Species/ Number per sex and group	Dose (mg/kg)/ Route	Duration	NOAEL (mg/kg)	Major findings
MICE					
Palm 1970 Non-GLP PH-43-65-61	Swiss mice/ 10	0,3,4.16,5.04,6/ Oral (gavage)	5 days	≈3 (LD_{50} 4.35)	>3: ↓body weight at day 8 Mean time to death: day 16
Palm 1970 Non-GLP PH-43-65-61	Swiss mice/ 10	0, 1.1, 1.61, 2.35, 3.42, 5/ i.p.	5 days	<1.1 (LD_{50} 2.48)	≥1.1: ↓body weight at day 8 Mean time to death: day 13

Study ID	Species/ Number per sex and group	Dose (mg/kg)/ Route	Duration	NOAEL (mg/kg)	Major findings
Reno 1983 (US GLP) 6133-101	$CD2F_1$ mice/ 15	0, 6.5, 8.2, 10.4, 13.2, 16.2, 21.2, 26.8/ i.v. (Lactated Ringer's)	5 days	<6.5 (LD_{50} 12.9)	≥6.5: ↓body weight Most deaths occurred days 4-12
Reno 1983 6133-101 (GLP) (dose range study) (1983)	CD2F1 mice 5/sex/group	1, 2, 10, 25, 50 i.v.(in lactated ringer's)	5 days		**Death: ≥ 25** (all animals), death occurred between day 4 and 7. Clinical signs
Vidaza-Tox-1452	CD-1mice (5/sex/group)	0 (0.9% w/v Sodium Chloride for Injection), 3, 6, and 12 mg/kg/day azacitidine i.v	7 days		**Deaths reported at 12 mg/kg/day,** significant clinical signs including decreased activity, slow breathing, abdominal distension, piloerection, and trembling. Body weight loss was also recorded. Decreased activity was observed in ≤ 6 mg/kg/day.
TOX-1475 2013 Intravenous (Bolus Injection) Toxicity Study of Azacitidine for Injection and Related Degradants (Including Oxazolidinone)	CD-1 mice (15/sex/group)	0 (0.9% w/v Sodium Chloride for Injection) or 3 mg/kg/day (with or without oxazolidinone) i.v	7 days		**No deaths reported,** ↓ reticulocytes, neutrophils, red cell mass, monocytes and eosinophils, platelets (females only) and lymphocytes
Azacitidine-TOX-2918 CC-17375 (oxazolidinone)	CD-1 mice (10/sex/group (M+F))	0 (0.9% Sodium Chloride for Injection), 0.63, or 1.26 mg/kg/day i.v (Slow Bolus)	7 days	The No Observed Adverse Effect Level (NOAEL) in this study was 1.26 mg/kg/day	**No Deaths Reported**, No Related clinical signs or effects on body weight, food consumption, ophthalmology, or organ weights, no macroscopic or microscopic findings.

Study ID	Species/ Number per sex and group	Dose (mg/kg)/ Route	Duration	NOAEL (mg/kg)	Major findings
Azacitidine-TOX-2756 CC-17375 (oxazolidinone)	CD-1 mice (10/sex/group (M+F))	0 (deionized water), 0.31, 0.62, or 1.23 mg/kg/day for a period of up to 21 days	21 days	NOAEL for males 1.23 mg/kg/day, for females 0.62 mg/kg/day	**No Deaths Reported**, no effects on clinical observations or ophthalmology At 1.23 mg/kg/day the following has been reported: • Increased ovary weights • Enlarged spleen • Microscopic changes including vaginal mucification, uterine hypertrophy, and mammary gland lobular hypertrophy/hyperplasia
DOGS					
Palm 1970 Non-GLP PH-43-65-61	Beagle dogs/ 1	0.28, 0.55, 1.1, 2.2, 4.4/ i.v.	5 days	0.28	0.55: ↓ WBC & RBC ≥1.1: ↑ SGPT ≥2.2: ↑ BUN 4.4: both died on day 4
Palm 1970 Non-GLP PH-43-65-61	Beagle dogs/ 1	0, 0.28, 0.55, 1.1/ i.v.	5 days x 2 cycles	0.28	0.28: ↑ WBC (one dog) 0.55: ↓ WBC, ↑ SGPT 1.1: 1M died on day 15
PH-43-65-61 Palm 1970 Non-GLP	Beagle dogs/ 1 (for each formulation)	0, 0.55/ i.v. (PVP vs. water)	5 days x 2 cycles	<0.55	↑ SGPT & BUN ↓ RBC No difference water-PVP
Popke, E 2007 GLP 1306-001	Beagle dogs/ 5	0, 0.2, 0.4, 0.8/ PO	14 days	0.2	PO ≥ 0.4 mg/kg/day → ↑ mortality, severe pancytopenia, cellular depletion in the bone marrow, and lymphoid depletion in the thymus, spleen, and lymph nodes.
Popke, E 1306-002 (2007)	Beagle dogs 3 females	0.8 oral (capsule)	2	**MTD: 0.8**	**0.8:** emesis and fecal changes
Monkey					

Study ID	Species/ Number per sex and group	Dose (mg/kg)/ Route	Duration	NOAEL (mg/kg)	Major findings
Palm 1972 GLP ADL-NCI-72-35	Rhesus monkey/ 1	0 (water), 0 (PVP), 0.28, 0.55, 1.1, 2.2/ i.v. (5-aza in PVP)	14 days	<0.28	≥0.28: ↓ WBC ≥1.1: Bone marrow hypoplasia Liver fatty metamorphosis 2:2: ↑ SGOT, SGPT & BUN

Genotoxicity

The applicant presented non-GLP studies conducted over the last three decades.

Table 3: Genotoxicity studies

Type of test/ Reference	Test system	Concentrations/ Concentration range/ Metabolising system	Results Positive/negative/equivocal
Gene mutations in bacteria/Podger, 1983	*Salmonella typhimurium* strains TA 98, TA 100, trpE8, trpE8 uvr, trp E8 recA, trpE8/pKM101	1, 2, 4, 6, 8, 10 µg/ plate/ without metabolizing system	Positive in all trpE8 strains except for trp E8 recA Negative in TA98 and TA100
Gene mutations in bacteria / Marquardt, 1977	*Salmonella typhimurium* strain TA 100	1, 10, 20, 40, 60, 80 µg/ plate	Positive
Gene mutations in bacteria / Ohta, 2000	*Salmonella typhimurium* strains TA 7002, TA 7004, TA 7005	1, 1,5 , 2, 5 µg/ plate	Negative
Gene mutations in bacteria/ Ohta, 2000	*Escherichia coli* strains WP3101P, WP 3102P, WP3103P, WP3104P, WP3105P	1, 1,5 , 2, 5 µg/ plate	At 5 µg/ plate Positive in strains WP3103P and 3104P
Gene mutations in bacteria/ Fucik, 1965	*Escherichia coli* strains WP14Pro$^-$ and WP2Try $^-$	0,4 and 4 µg/ml +/- S9	Positive in WP14Pro$^-$ (uridine and cytidine neutralized mutagenic effect) Negative with WP2Try $^-$
Gene mutations in bacteria/ Watanabe, 1994	*Escherichia coli* strains CC101-106	1 – 10 µg/ plate	Positive in CC103, 104, 105
Gene mutations in mammalian cells/ Amacher, 1987	L5178Y mouse lymphoma cells	0,005 – 0,15 µg/ml +/- S9	Positive
Gene mutations in mammalian cells/ Li, 1970	L1210 Mouse leukemia cells	1- 5 µg/ml	Positive
Clastogenicity assay / Call, 1986	Human lymphoblasts TK6 cells	0 – 10 µM for 24 hours	Positive (mutagenic at 0,1 µM/ clastogenic at 0,5 µM)
Clastogenicity assay/ Stopper, 1992	Syrian hamster embryo fibroblasts	0,2 – 10 µM	Positive for induction of micronuclei (1-10 µM) Negative for UDS
Clastogenicity assay/ Stopper, 1993	L5178Y mouse lymphoma cells	0,1 – 5 µM	Positive (azacitidine induced micronuclei, increase of kinetochores)

Carcinogenicity

Long-term studies

The potential carcinogenicity of azacitidine was evaluated in mice and rats as shown in the Table 11 below. The studies presented were not conducted in accordance with current GLP or ICH guidelines.

Table 4: **Carcinogenicity studies**

Reference/ GLP status	Dose/Route	Study duration	Species/Number of animals	Major findings
Cavaliere, 1987 Non-GLP	0 and 2 mg/kg/week IP	50 weeks	BALB/c mice/ 50/ sex/ group	Significant increase in the incidence of tumors in lymphoreticular system, lung, mammary gland and skin
National Cancer Institute, 1978 Non-GLP	2,2 and 4,4 mg/kg/ IP (3x/week)	52 weeks (with a 29-30 week observation period)	B6C3F1 mice/ 35/ sex/ group	At 2,2 mg/kg Tumors of hematopoietic system (F) At 4,4 mg/kg Bone marrow atrophy (M + F)
National Cancer Institute, 1978 Non-GLP	2,6 and 5,2 mg/kg IP (3x/week)	34 weeks (with a 46 or 47 week observation period)	Sprague-Dawley rats / 35/ sex/ group	At 5,2 mg/kg Decreased life span
Carr, 1984 Non-GLP	2,5 and 10 mg/kg 2x/week IP	9-18 Months	Male Fischer rats	• Increased incidence of testicular tumors • High incidence of interstitial cell tumors

Short or medium-term studies

The potential carcinogenicity of azacitidine was evaluated in mice as shown in the following Table 12. The study was not conducted in accordance with current GLP or ICH guidelines.

Table 5: Carcinogenicity studies (cont)

Stoner, 1973	0, 0.033, 0.062, and 0.090 g/kg 3x/week	8 weeks	A/He mice	• At highest dose Tumours in lung detected

Reproduction Toxicity

The applicant submitted non-GLP studies on fertility and embryo-fœtal development performed in mice (i.p.) and rats (i.p.).

Table 6: **Reproduction toxicity studies**

Study type/ Study ID / GLP	Species/ Number/ group	Route & dose (mg/kg)	Dosing period	Major findings
Male fertility and early embryonic development/ Doerksen, 1996 Non-GLP	Sprague Dawley rats/ 8 males/ group	2.5, 4 or 5 IP (3x / week)	4, 11 or 16 weeks	2,5 mg/kg for 11 weeks decreased body weight, decreased weight of testes and epididymides decreased hematocrit and increased embryo loss. 5,0 mg/kg for 11 weeks decreased body weight, decreased weight of testes and epididymides, decreased sperm count, decreased hematocrit and decreased pregnancy rates.

Male fertility and early embryonic development/ Doerksen, 2000 Non-GLP	Sprague Dawley rats/ 6 males/ group	2.5, 4 or 5 IP (3x / week)	6 or 11 weeks	2,5 mg/kg for 11 weeks decreases in body weight, epididymides weight and sperm DNA methylation. 4 mg/kg for 11 weeks decreases in body weight, testes and epididymides weight, and sperm DNA methylation with histologic evidence of degeneration in the testes and reduced sperm in the epididymides.
Embryo-fœtal development/ Rosen, 1990 Non-GLP	Sprague Dawley rats/ 5-6 females/ group	0,5 ; 1 ; 1 ; 2 IP	Single dose GDays 9, 10, 11 or 12	At 1 and 2 mg/kg on GD 9 or GD 10 Embryonic death 0,5 – 2 mg/kg on GD 10, GD 11 or GD12 High incidence of fetal abnormalities
Embryo-fœtal development/ Cummings, 1994 Non-GLP	Holtzman rats/ 8 females/ group	0,15 / 0,3 / 0,6/ 1,2 IP	GDays 1-8	0,3 – 1,2 mg/kg Dose-proportional embryolethality and resorptions at GD 20 Increase incidence of fetal malformations (microphtalmia and exencephaly)
		0,5-1 IP	GD 1-3	No effects
		0,5-1 IP	GD 4-8	At 1 mg/kg Increased embryolethality and resorptions on GD 20
Embryo-fœtal development/ Takeuchi, 1985 Non-GLP	S1c: ICR mice/ 10 females/ group	1 IP	Single dose GD 7,5	Loss of germinal cells in the neurectoderm resulting in high incidence of exencephalic offspring
Embryo-fœtal development/ Schmahl, 1984 Non-GLP	NMRI mice/ 26-32 females/ group	2 IP	Single Dose on GD 10	Increase embryolethality (43,6% at 2 mg/kg) Numerous malformations
Embryo-fœtal development/ Schmahl, 1984 Non-GLP	NMRI mice/ 21-26 females/ group	0,5 / 1/ 2 / 4 IP	Single dose on GD 12	dose dependent increase of embryolethality (11,2% at 2 mg/kg / 42,2% at 4mg/kg)
Embryo-fœtal development/ Schmahl, 1984 Non-GLP	NMRI mice/ 21-26 females/ group	0,5 / 1/ 2 / 4 IP	Single dose on GD 14	dose dependent increase of embryolethality (11,8 % at 2 mg/kg / 42,2% at 4 mg/kg)
Embryo-fœtal development/ Svata, 1966 Non-GLP	AKR mice/ 5 or 10 females/ group	2,5 IP	3 or 6 days	Embryolethality
Embryo-fœtal development/ Langman 1971 Non-GLP	DUB/ICR mice/ 6 or 15 females/ group	4 IP	Single dose on GD 15	3-4 hours after treatment abnormal mitotic figures, chromosomal changes and neuronal deficits in the neocortex
Embryo-fœtal development/ Langman 1971 Non-GLP	DUB/ICR mice/ 18 females/ group	2 IP	GD 13 - GD 15	Neuronal deficits in neocortex and hippocampus
Embryo Survival Seifertova, 1976	Mice strain II	0, 1, 3 5 IP	GD 11 GD 13	All doses: - decreased embryo survival, increased resorption and smaller litter size

Non-GLP				

Toxicokinetic data

Kinetics of azacitidine after a single dose were evaluated in a 2-day and repeat dose 14-day oral studies in dogs.

Some variability is observed in the plasma concentrations between males and females but no gender differences are observed following PO administration. Systemic exposure increases with increasing dose with little evidence of accumulation following repeated administration.

The applicant records the no adverse effect level (NOAEL) to be 0.2 mg/kg/day, while mean steady-state exposure (AUC) at this dose level was 0.223 h*ug/ml in females and 0.148 h*ng/ml in males.

Table 2. Summary Azacitidine Toxicokinetic Parameters on Day 14 (or Day 10) Following Multiple-Dose Administration of 0.2, 0.4, and 0.8 mg/kg/day Azacitidine Once Daily Orally via Gelatin Capsules to Male and Female Dogs

	Group (n)	Dose (mg/kg/day)	t_{MAX} (hr)	C_{MAX} (µg/mL)	AUC_T (µg*hr/mL)	AUC (µg*hr/mL)	$t_{1/2Z}$ (hr)	Rac
Males								
Mean	2 (n=5)	0.2	0.6	0.129	0.148	0.168	0.821	0.949
SD			0.224	0.021	0.021	0.023	0.05	0.298
Mean	3 (n=5)	0.4	0.803	0.251	0.344	0.362	0.792	1.49
SD			0.277	0.056	0.054	0.057	0.081	0.839
Mean	4 (n=5)	0.8	0.6	0.88	0.997	1.32	0.829	1.35
SD			0.224	0.18	0.21	0.33	0.13	0.716
Females								
Mean	2 (n=5)	0.2	0.703	0.152	0.223	0.239	0.993	0.95
SD			0.279	0.075	0.115	0.119	0.454	0.461
Mean	3 (n=5)	0.4	0.707	0.313	0.478	0.501	0.883	1.66
SD			0.283	0.113	0.16	0.166	0.069	0.732
Mean	4 (n=5)	0.8	0.746	0.761	0.971	1.33	0.843	1.53
SD			0.294	0.147	0.205	0.36	0.14	0.612

[a] Day 14 (or Day 10): AUC = AUC_τ or AUC_{ALL}.

Source: Supportive Tables ST-37 to ST-45.

Local Tolerance

Local tolerance studies have been conducted in rabbits and hamsters. The studies are summarized as follows:

Study RIPS-CIPA-102816-13-76: One, 3, and 9% azacitidine in 1% methyl cellulose was applied to the skin of New Zealand White rabbits. The application sites were cleaned with water 24 hours after application and examined after 30 minutes, 48 hours, and 72 hours later including microscopic evaluation at 72 hours. Mild skin irritation reported at a concentration of 9 % of azacitidine by Draize method.

Study PH-43-65-61: Azacitidine up tot concentrations of 21 mg/ml in Sudak's buffer applied topically to hamster cheek pouches caused a slight temporary stickiness of white blood cells to endothelium, and venous blood flow was also reduced for a short time (5-6 min.).
Intravenous administration of azacitidine (up to 250 mg/kg) in the jugular vein induced a moderate to severely reduction in the arteriole and venule blood flow, but there was no evidence of thromboembolism.

Study ADL-NCI-72-38: Azacitidine formulated with polyvinylpyrrolidone (PVP) in Sudak's buffer (3.5-20 mg/ml) applied topically to hamster cheek pouches temporarily reduced arteriole and venule blood at all concentrations tested. There was no evidence of thromboembolism, also no stickiness of leukocytes was observed.

I.v. injections up to 125 mg/kg in PVP/ Sudak's buffer induced slight to severe reduction sin venule blood flow, and moderate to severe reduction in arteriole flow. The effects were immediate and transitory. Thromboembolism was not seen.

Other toxicity studies

Not applicable

2.3.5. Ecotoxicity/environmental risk assessment

Table 7: Summary of main study results

Substance (INN/Invented Name):			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	Data based on Section 3.2.S.1.3 of the Marketing Authorisation Application for Onureg	Between -0.1 and 0.2 at pH between 2 and 12 (at 25°C)	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	An assessment for persistence, bioaccumulation and toxicity (PBT) was not performed as the logKow <3	not B
	BCF	N/A as logKow <3	not B
Persistence	DT50 or ready biodegradability	N/A as logKow <3	not P
Toxicity	NOEC (OECD 201) (OECD 211) (OECD 210) (OECD 209; EC_{50})	 31 **µg/L** 730 **µg/L** 1000 **µg/L** >100,000 **µg/L**	not T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, refined	0.00025	µg/L	< 0.01 (>0.01 =threshold) [N]
Other concerns (e.g. chemical class)			(N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 121 …	K_{oc} = <10,000 L/kg,	<33 L/kg ((Oudhoff, 2009a)).
Ready Biodegradability Test	OECD 301 B	Biodegradable	

Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = $DT_{50, sediment}$ = $DT_{50, whole\ system}$ = % shifting to sediment =			Not required if readily biodegradable DT90 has Not been established. Based on the decrease in azacitidine concentration in the algal growth inhibition test, the DT90 is estimated might be in the order of magnitude of a few days
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	31	µg/L	*Selenastrum capricornutum*
Daphnia sp. Reproduction Test	OECD 211	NOEC	730	µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	1000	µg/L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	>100 ,000	µg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/kg	%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$			for all 4 soils
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect		mg/ kg	
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC		mg/ kg	
Earthworm, Acute Toxicity Tests	OECD 207	NOEC		mg/ kg	
Collembola, Reproduction Test	ISO 11267	NOEC		mg/ kg	
Sediment dwelling organism		NOEC		mg/ kg	species

2.3.6. Discussion on non-clinical aspects

The applicant has presented a non-clinical package consisting mainly of studies reported in published literature, accompanied by sponsored studies. It has to be noted that most of the non-clinical studies were conducted in the 1960s, 1970s and 1980s prior to the implementation of International Conference on Harmonisation (ICH) guidelines and Good Laboratory Practice (GLP) regulations. Hence, there are intrinsic flaws in the non-clinical data presented due to the lack of details available concerning the quality of information gathered. However, given the extensive clinical experience and the overall reliability of the pre-clinical package, the absence of GLP compliance is accepted.

Although the submitted toxicity data deviates from the guidelines at several points, there are extensive clinical experiences on azacitidine toxicities in humans. Studies have been performed using the oral route in the data package submitted and although repeated dose studies were conducted, these were not completely in line with the proposed clinical use.

Data on exposure was generally not available within the toxicity studies. The number of animals/sex/group was generally less than required for determining biological relevance of the findings.

There are deficiencies in the non-clinical data, yet there are adequate clinical data to provide the insight on azacitidine toxicities in humans. Taken all together, systemic toxicity of azacitidine is adequately characterised with the results obtained in IV, IP and PO administration in sensitive animal species (dog and monkey).

The results show that primary target organs of toxicity appear to be consistent between the studies. The largest limitation in the data package submitted from a toxicological perspective, is that unexpected toxicities due to prolonged exposure may have been missed by the submitted non-clinical studies; however, extensive clinical safety data of azacitidine adequately supplemented to any lack of unexpected toxicities in animals after prolonged exposures.

Toxicity was reported in the lymphoid system, bone marrow, liver, gland/lumen dilation and single cell necrosis in mucosal crypts of small and large intestines and/or centrilobular hepatocellular vacuolation. Possible toxicity of the kidneys cannot be ruled out. Deaths reported, occurred several days up to several weeks after start of treatment. Generally toxic effects were reversible with recovery evident in surviving animals. In the repeated dose studies severe toxicity was seen at doses lower than the approved oral azacitidine dose in humans. An explanation for this difference could be that there might be a higher exposure in the test animals due to reduced activity of the enzyme, cytidine deaminase, compared to humans. Cytidine deaminase is involved in the deamination of azacitidine which is the primary pathway for the breakdown of azacitidine.

Non concerning variability has been reported in the plasma concentrations of male and female dogs, but the data indicate that there are no gender differences observed following PO administration. Some slight differences in toxic effect in dogs between males and females were reported, however these are minor and not of a concern.

Genotoxicity studies cited in this dossier were not in accordance with current ICH guideline, but all the data indicate that azacitidine induces gene mutations and chromosome aberrations in vitro. There were no in vivo genotoxicity/clastogenicity studies.

Despite several gaps in the design of the studies (low animal number, non-GLP) the genotoxicity studies indicate that azacitidine is a potential carcinogen. Azacitidine induces both gene mutations and chromosomal aberrations in bacterial and mammalian cell systems *in vitro*. The potential carcinogenicity of azacitidine was evaluated in mice and rats. Azacitidine induced tumours of the haematopoietic system in female mice, when administered intraperitoneally 3 times per week for 52 weeks. An increased incidence of tumours in the lymphoreticular system, lung, mammary gland, and skin was seen in mice treated with azacitidine administered intraperitoneally for 50 weeks. A tumorigenicity study in rats revealed an increased incidence of testicular tumours. The data also suggest that low doses of azacitidine can even induce skin tumours (especially squamous cell carcinomas).

Single doses of azacitidine can be embryolethal and teratogenic in rats and mice when given during organogenesis. Early embryotoxicity studies in mice revealed a 44% frequency of intrauterine embryonal death (increased resorption) after a single IP injection of azacitidine during organogenesis. Developmental abnormalities in the brain have been detected in mice given azacitidine on or before closure of the hard palate. In rats, azacitidine caused no adverse reactions when given pre implantation, but it was clearly embryotoxic

when given during organogenesis. Foetal abnormalities during organogenesis in rats included: Central nervous system (CNS) anomalies (exencephaly/encephalocele), limb anomalies (micromelia, club foot, syndactyly, oligodactyly) and others (microphthalmia, micrognathia, gastroschisis, oedema, and rib abnormalities) (See SmPC Section 5.3)

Also, paternal treatment with azacitidine resulted in dose-dependent effects on spermatogenesis and subsequent progeny outcome at doses causing no/low systemic toxic effects. Administration of azacitidine to male mice prior to mating with untreated female mice resulted in decreased fertility and loss of offspring during subsequent embryonic and postnatal development. Treatment of male rats resulted in decreased weight of the testes and epididymides, decreased sperm counts, decreased pregnancy rates, an increase in abnormal embryos and increased loss of embryos in mated females (See SmPC section 5.3).

The potential risk of developmental toxicity for humans is unknown. Based on results from animal studies and its mechanism of action, Onureg is not recommended during pregnancy (See SmPC section 4.6).

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical documentation submitted was considered adequate.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Type of Study	Study Identifier	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Controlled Clinical Studies Pertinent to the Claimed Indication	CC-486-AML-001	To evaluate whether maintenance therapy with CC-486 improved OS compared with placebo in subjects with AML, ≥ 55 years of age, who had achieved first CR or CRi after induction with intensive chemotherapy with or without consolidation chemotherapy	Phase 3, randomized, placebo-controlled, double-blind, international study 1. Experimental Arm, CC-486 300 mg plus BSC 2. Control Arm, placebo plus BSC	CC-486 300 mg or placebo QD for 14 days of repeated 28-day cycles	**Enrolled:** N = 472 **Treated:** N = 469 Experimental Arm: N = 236 Control Arm: N = 233	AML, ≥ 55 yrs, either newly diagnosed AML or AML secondary to prior MDS or CMML	**Treatment Phase:** until relapse, AE discontinuation withdrawal, eligibility for HSCT, or death **Follow-up Phase:** until death, withdrawal, study end, or LTF	Enrollment completed; study ongoing Interim report
Patient PK and Initial Tolerability Study Reports	CC-486-AML-002	To determine the MTD of CC-486 in subjects with AML or MDS after allogeneic HSCT	Phase 1/2 dose and schedule finding study	CC-486 150, 200, or 300 mg QD for 7 or 14 days of repeated 28-day cycles	**Enrolled:** N = 31 **Treated:** N = 30 Subjects with AML: N = 26 Subjects with MDS: N = 4	MDS or AML after HSCT, ≥ 18 yrs	Up to 12 cycles of treatment	Study completed Full report
Patient PK and Initial Tolerability Study Reports	CC-486-MDS-001	To identify the MTD of CC-486 in Japanese subjects with hematological neoplasms	Phase 1, open-label, dose-escalation study	CC-486 100, 200, or 300 mg for 14 or 21 days of repeated 28-day cycles	**Enrolled:** N = 2 **Treated:** N = 2	Hematological neoplasms	Until progressive disease or discontinuation for any reason	Study completed Full report

Type of Study	Study Identifier	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Comparative BA and Bioequivalence Study Reports	AZA-MDS-004	To evaluate the PK of CC-486 administered QD as two 150-mg tablets (including the effect of food), to evaluate the bioavailability of CC-486 administered QD as two 150-mg tablets relative to three 100-mg tablets, and to evaluate the effect of gastric acid pH modulation, through a proton pump inhibitor, on the PK of CC-486	Phase 1, open-label PK study	**PK Part I**: CC-486 300 mg QD for 3 total doses (3 × 100 mg tablets fasted, 2 × 150 mg tablets fasted, 2 × 150 mg tablets fed) in 1 of 6 possible dosing sequences **PK Part II**: CC-486 300 mg QD (2 × 150 mg tablets) fasted on Day 1; omeprazole 40 mg QD on Days 2 to 4, and sequential omeprazole 40 mg QD plus CC-486 300 mg fasted on Day 5 **Extension Phase**: CC-486 300 mg (3 × 100 mg) for 21 days of repeated 28-day cycles	**Enrolled:** N = 34 **Treated:** N = 32	MDS, CMML, or AML, ≥ 18 yrs	Part I: 3 doses of CC-486 over a maximum of 10 days; Part II: 5 days; Extension period: Until discontinuation due to disease progression, unacceptable toxicity or any other reason.	Study completed Full report

Type of Study	Study Identifier	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Patient PK and Initial Tolerability Study Reports	AZA-MDS-005	To evaluate the tolerability of a 300 mg dose of CC-486 in Japanese patients with MDS	Phase 1, open-label PK study	CC-486 Cycle 1: Single CC-486 200 mg or 400 mg dose Day 1, then 300 mg QD CC-486 dose on Days 4-24 with 7-day rest/31-day cycle	**Enrolled:** N = 5 **Treated:** N = 5	MDS	Until any discontinuation criteria are met	Study completed Full report
Patient PK and Initial Tolerability Study Reports	AZA PH US 2007 CL 005	To determine the MTD, DLTs, the safety profile, and to evaluate the PK behavior and PD effects of azacitidine administered orally and SC	Phase 1, open-label, sequential design, dose-escalation study	CC-486 and SC azacitidine **Part 1** – Cycle 1: SC azacitidine 75 mg/m^2 QD for first 7 days of the 28-day cycle Cycle 2+: CC-486 starting dose 120 mg/day for 7 days; dose escalated until MTD **Part 2** – CC-486 300 mg QD × 14/28 days; 200 mg BID × 14/28 days; 300 mg QD × 21/28 days; and 200 mg BID × 21/28 days Dose modification per protocol criteria	**Enrolled:** N = 131 **Treated:** N = 131	MDS, CMML, or AML, ≥ 18 yrs	Subjects could continue to receive study drug until disease progression, or other significant AEs.	Study completed Full report

Patient PK and Initial Tolerability Study Reports	AZA PH US 2008 CL 008	To investigate the PK of CC-486 including the effect of food, to determine the oral bioavailability of up to 6 different oral formulations relative to SC azacitidine, to assess the safety and tolerability of CC-486, and to estimate the dose for a given oral formulation that would yield similar exposure to 75 mg/m^2 SC dosing	Phase 1, open-label, dose ranging study	CC-486 and SC azacitidine **Part 1 PK Phase (Cycle 1)**: 75 mg/m^2 SC on Day 1 and 15; CC-486 in increasing doses on Days 3 and 5, and at doses calculated to deliver 80% and 120% of the SC exposure (AUC) on Days 17 and 19. **Part 1 Treatment Phase (Cycles 2+):** CC-486 QD on Days 1-7 of repeated 28-day cycles **Part 2 PK Phase (Cycle 1)**: CC-486 600 mg QD on Days 1-7 of repeated 28-day cycles. **Part 2 Treatment Phase (Cycles 2+)**: CC-486 600 mg QD on Days 1-7 of repeated 28-day cycles	**Enrolled:** N = 31 **Treated:** N = 29	MDS, CMML, AML, lymphoma, or MM	**Part 1 PK**: 1 cycle **Part 2 PK Phase**: 1 cycle **Treatment Phase**: Optional continuation of treatment until discontinuation due to disease progression, unacceptable toxicity or any other reason	Study completed Full report
Uncontrolled Clinical Studies	CC-486-GEN-001	To evaluate the long-term safety of CC-486 in subjects who have received	Phase 2, open-label, single-arm, rollover study	CC-486 at the dose and schedule received at the time of discontinuation from the	**Enrolled:** N = 4 **Treated:** N = 4	Solid tumors or hematological disorders	Until disease relapse or progressive disease, or a withdrawal criterion is met, or until CC-486 becomes	Study ongoing

Type of Study	Study Identifier	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
		CC-486 as monotherapy in other Celgene-sponsored clinical trials and whom the investigators feel may derive clinical benefit from continuing treatment with CC-486		parent study			commercially available	
Controlled Clinical Studies Pertinent to the Claimed Indication	AZA-MDS-003	To evaluate RBC transfusion independence in the 2 treatment arms	Phase 3 multicenter, randomized, double-blind, placebo-controlled study 1. Experimental Arm, CC-486 300 mg plus BSC 2. Control Arm, placebo plus BSC	CC-486 300 mg × 21/28 days As of 01 Feb 2018 (Protocol Amendment 3), dosing schedule for Cycles 1 and 2 was changed to 14 days of a 28-day cycle	**Enrolled:** N = 216 **Treated:** N = 216 Experimental Arm: N = 107 Control Arm: N =109	RBC transfusion-dependent anemia and thrombocytopenia due to IPSS lower-risk MDS	As long as subjects derive benefit or until discontinuation criteria are met	Study ongoing Interim report

Reports of Bioanalytical and Analytical Methods for Human Studies	AZA-ST-001	The primary objective for Part 1 of the study was to evaluate the safety and define the MTD or the MAD of CC-486 as a single agent and in combination with carboplatin (CBDCA) or nab-paclitaxel (referred to as ABI-007) in subjects with relapsed or refractory solid tumors. The primary objective for Part 2 of the study was to assess the safety and tolerability of CC-486 administered at the RP2D, either alone or in combination with CBDCA or ABI-007 in tumor-specific expansion cohorts.	Phase 1, open-label, 3-arm study in 2 parts	**Arm A**: CC-486 + carboplatin (CBDCA) **Arm B**: CC-486 + ABI-007 **Arm C**: CC-486 as a single agent for the first 7 days of study. Beginning on Cycle 1, Day 8, subjects in Arms A and B will begin combination treatment with CBDCA or ABI-007, respectively. Subjects in Arm C will receive single agent CC-486 in all cycles until they experience unacceptable toxicity or disease, whichever occurs first	**Enrolled:** N = 41 **Treated:** N = 41	solid tumors	Until subject experienced unacceptable toxicity or progressive disease	Study completed Full report
Uncontrolled Clinical Studies	CC-486-NPC-001	To evaluate the efficacy of CC-486 in subjects with NPC	Phase 2, single-arm study	CC-486 300 mg × 14/21 days	**Enrolled:** N = 36 **Treated:** N = 36	NPC	Subjects were treated until radiologic disease progression. Median duration of	Study completed Full report

Type of Study	Study Identifier	Primary Objective (s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
							study treatment was expected to be 6 months.	

Type of Study	Study Identifier	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Bioequivalence and Food Effect Study Reports	CC-486-CAGEN-001	**PK Stage I:** to evaluate the bioequivalence of CC-486 when administered once daily as 1 x 300 mg tablet (F9) relative to 2 x 150 mg tablets (F8) **PK Stage II:** to evaluate the food effect on the bioavailability of CC-486 when administered once daily as 1 x 300 mg tablet (F9 only) in a fed state (high-fat and high-caloric meal) relative to a 1 x 300 mg tablet (F9 only) in a fasted state	Phase 1, open-label PK study	**PK Stage I: Bioequivalence:** CC-486 300 mg orally on each of two study days for 2 total doses, as one 300 mg tablet followed by 2 × 150 mg tablets or vice versa **PK Stage II: Food Effect:** CC-486 300 mg orally on each of two study days for 2 total doses, as one 300 mg tablet with food followed by 300 mg tablets fasting or vice versa **Optional Extension** (after completion of PK Stage I or Stage II): azacitidine injectable 75 mg/m2 IV or SC for 7 days every 4-week cycle for ≤ 6 cycles (per prescribed label and investigator discretion)	**PK Stage I:** *Enrolled*: N = 30 *Treated:* N = 30 **PK Stage II:** *Enrolled*: N = 59 *Treated:* N = 57 **Optional Extension:** *Enrolled*: N = 74 *Treated:* N = 74	Subjects with hematologic or solid tumor malignancies for which no standard treatment exists, or which has progressed or recurred following prior therapy, ≥ 18 yrs	**PK Stage I:** 2 doses of CC-486 over a maximum of 10 days; **PK Stage II:** 2 doses of CC-486 over a maximum of 10 days; **Optional Extension** (after completion of PK Stage I or Stage II): up to 6 cycles of Vidaza® per prescribed label	Study completed Full report

Type of Study	Study Identifier	Primary Objective (s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Controlled Clinical Studies Pertinent to the Claimed Indication	AZA-AML-001	To compare the efficacy and safety of azacitidine versus CCR for the treatment of older subjects with newly diagnosed AML	Phase 3, open-label, randomized, parallel-group study 1. Experimental Arm, Azacitidine 75 mg/m^2/day SC 2. Control Arm, CCR assigned by Investigator prior to randomization	Azacitidine 75 mg/m^2/day SC for 7 days of every 28-day cycle	**Enrolled:** N = 488 **Treated:** N = 488 Experimental Arm: N = 241 Control Arm: N =247	Subjects with newly diagnosed de novo or secondary AML and were not eligible for HSCT, ≥ 65 yrs	12 months	Study completed Full report

2.4.2. Pharmacokinetics

The PK of Onureg was investigated in 11 studies in subjects with hematologic malignancies (MDS, CMML, AML, lymphoma, or MM) at doses ranging from 120 mg to 600 mg and compared to the SC azacitidine starting dose of 75 mg/m2. Based on data from these studies, oral azacitidine PK characteristics in terms of absorption, distribution, metabolism and elimination (ADME) were determined. Intrinsic factors (age, gender, race, weight, renal and hepatic labs) and their impact on azacitidine PK were assessed by Population PK (PopPK) modelling (CC-486-MPK-001), which included 286 subjects with 1933 concentration records from studies AZA-MDS-004, CC-486-CAGEN-001, and CC-486-AML-001.

Absorption

The PK of azacitidine following IV and SC administration has been previously characterized and demonstrated rapid and nearly complete absorption of azacitidine following SC administration with T_{max} occurring within 30 minutes and a bioavailability of 89% relative to IV administration. Similarly, absorption of azacitidine after oral administration was rapid, with C_{max} occurring at approximately 1-hour post-dose. The area under the curve (AUC) generally increased with dose, although high inter-subject variability in azacitidine exposures was observed (percent coefficient of variation [%CV] range of 30 to 74%). The C_{max} and AUC parameters are further corroborated by PopPK analysis. No accumulation of azacitidine is observed after multiple doses. Oral bioavailability relative to subcutaneous administration was 11.5% at a dose of 360 mg for Formulation F6, which was chosen for further clinical development.

During the biopharmaceutic development related to absorption and formulation development 3 primary tablet formulations were used: F6, F8, and F9 (F9 being the market image). Bioavailability with respect to SC administration was used as a guide for formulation development.

Final market image formulation F9 has been shown to be bioequivalent to earlier formulation F8 used in earlier clinical trials, thus validating the formulation development process.

No clinically meaningful change in the PK of azacitidine was observed upon oral administration with a high-fat, high-calorie meal, thus, CC-486 can be taken with or without food. Absorption of azacitidine is not affected by changes in gastric pH; no dose modification is required when co-administered with a PPI or other pH modulators (AZA-MDS-004).

Distribution

Following oral administration, the geometric mean apparent volume of distribution of azacitidine (V/F) determined directly in one study is 881 L (12.6 L/kg for a 70 kg person) at a dose of 300 mg further confirmed by PopPK analysis (889L)The plasma protein binding of azacitidine is approximately 6-12% and independent of azacitidine concentrations.

Elimination

From early radiotracer studies in patients with advanced cancer following both IV and SC administration, the kidneys excrete azacitidine and/or its metabolites, with 50% to 100% of the injected radioactivity recovered in urine over a 48- to 72-hour period after dosing.

The mean terminal half-life of azacitidine after oral administration of 300 mg is approximately 0.5 hours (similar to that after IV [0.36 hours] and SC [0.69 hours] dosing). The geometric mean apparent clearance is 1242 L/h (CC-486-CAGEN-001).

The following Table 15 summarises the main PK parameters from oral azacitidine.

Table 8: CC-486 Plasma Pharmacokinetic Parameters Following 300mg Dose (Geometric Mean, Geometric %CV)

Single Dose	$AUC_{0-\infty}$ (ng•h/mL)	AUC_{0-t} (ng•h /mL)	C_{max} (ng/mL)	T_{max}[a] (h)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)
AZA PH US 2007 CL 005 (N = 5; F1-3)	268.3 (37.6)	269.3 (37.9)	143.1 (9.2)	1.483 (1.00, 2.00)	0.542 (20.9)	1118.2 (37.6)	874.7 (39.8)
AZA PH US 2007 CL 005 (N = 25; F6)	157.4 (74.0)	157.4 (74.6)	101.1 (73.0)	1.00 (0.467, 2.00)	0.508 (29.7)	1905.7 (74.0)	1396.4 (81.8)
AZA-MDS-004 (N=16; F6 and F8)	303.1 (81.3)	301.0 (81.9)	158.2 (86.2)	1.00 (0.50, 2.50)	0.5 (32.6)	989.7 (81.3)	738.8 (88.1)
CC-486-CAGEN-001 (N = 30; F8 and F9)	241.6 (64.5)	239.1 (65.2)	145.1 (63.7)	1.0 (0.50 – 2.5)	0.492 (26.9)	1242 (64.5)	881.1 (67.4)
Population PK							
CC-486-AML-001 (N = 227; F8)	NC	192.0 (41.26)	87.15 (42.3)	0.749 (0.358, 2.28)	0.438 (68.1)	1562 (41.3)	988 (57.2)

%CV = percent coefficient of variation; AUC_{0-t} = area under the plasma concentration-time curve from time 0 to the last quantifiable concentration; $AUC_{0-\infty}$ = area under the plasma concentration-time curve from time 0 extrapolated to infinity; CL/F = apparent clearance from plasma after oral administration; C_{max} = maximum observed plasma concentration; N = Number of subjects; NC = not calculated; T_{max} = time to maximum plasma concentration; $t_{1/2}$ = terminal elimination half-life; Vz/F = apparent volume of distribution.

[a] T_{max} is summarized by median and range (minimum – maximum)

Dose proportionality and time dependencies

In general, and despite the large variability, oral Azacitidine PK seems to show linearity in doses between 120 mg and 600 mg. With a mean elimination half-life of azacitidine after oral administration ranging from approximately 0.5 to 1 hour, there is no accumulation in a once daily regime. However, the drug is administered during 14 to 21 days in a 28 days cycle.

Based on data from different routes of administration and formulations, showing a lack of relevant PK differences between days of treatment, there is no time dependency in azacitidine PK, in line with the fact that cytidine deaminase is not known to be induced and there are not many examples of its inhibition.

Special populations

Renal impairment

The influence of renal impairment on the PK of azacitidine was evaluated in six cancer subjects with normal renal function (CLcr > 80 mL/min) and six subjects with severe renal impairment (CLcr < 30 mL/min) following daily SC dosing at 75 mg/m2/day (AZA PH US 2007 PK 006). Severe renal impairment increased azacitidine exposure by approximately 70% after single and 41% after multiple subcutaneous administrations. Moreover, creatinine clearance was identified as a significant covariate on CL/F of CC-486 in the final PopPK model.

Impaired hepatic function

A clinical study to evaluate the effect of hepatic impairment on oral azacitidine PK has not been conducted. PopPK analysis determined that AST (8 to 155 U/L) and ALT (5 to 185 U/L) did not have clinically meaningful effects on the pharmacokinetics of oral azacitidine.

Additional PopPK analysis was conducted according to the NCI-ODWG hepatic impairment criteria. The effect of mild hepatic impairment was evaluated and did not improve the model fitting statistically, and therefore does not impact the clearance or exposure of azacitidine in a clinically relevant manner.

Age, Body Weight, Gender and Race

In a PopPK analysis based on cumulative data from 286 subjects who received oral azacitidine, intrinsic factors of gender, age (46 to 93 years), race (92% white), body mass index (BMI [15.7 to 51.7 kg/m2]) and body weight (39.3 to 129 kg) were examined and shown not to be clinically significant covariates influencing azacitidine exposure. As a limited number of non-white subjects were available for PopPK analysis, race covariate analysis results should be interpreted with caution. Only 2.3% of subjects in PopPK analysis were of Asian descent, and results from studies exploring the PK in and Asian-Pacific Island subjects were inconclusive due to high variability and small number of subjects enrolled. The safety and efficacy of oral azacitidine in children aged 0-17 years have not yet been established.

Special populations

Table 9: Number of Elderly Patients Included in the Population PK Analysis

	Age 65-74 **(Older subjects number/total number)**	**Age 75-84** **(Older subjects number/total number)**	**Age 85+** **(Older subjects number/total number)**
Population PK analysis	161/286	44/286	5/286

PK = pharmacokinetic

Pharmacokinetic interaction studies

In vitro drug-drug interaction studies demonstrate that azacitidine is not an inhibitor of cytochrome P450 (CYP) 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4, nor an inducer of CYP 1A2, 2C19, or 3A4/5. Azacitidine is not metabolized by CYPs. Hence azacitidine is unlikely to have any clinically relevant interactions when co-administered with CYP substrates, inducers or inhibitors. No UGT inhibition studies were performed for azacitidine. However, none of the major elimination pathways of the azacitidine is direct glucuronidation. It is also acknowledged that both the C_{max} and exposure are low and elimination is very fast. Taking into consideration the general characteristics of the UGT enzymes, and also according to the Guideline on the Investigation of Drug/Drug Interactions, the lack of in vitro inhibition studies is acceptable as a relevant DDI interaction through UGT inhibition is unlikely to occur. Azacitidine is not a P-gp substrate or inhibitor and is

unlikely to produce any clinically relevant interactions with P-gp. Azacitidine is not an inhibitor of BCRP, OATP1B1, OATP1B3, OAT1, OAT3, or OCT2 and is unlikely to interact with the substrates of these transporters. However, a decrease in CYP3A4/5 activity was observed with high (100 uM) concentrations that could be explained by inhibition of protein synthesis. However, it has been demonstrated that, at clinically relevant concentrations (1 and 10 μM), the decrease in CYP3A activity was minimal (<13%). Therefore, the suppression of CYP3A by azacitidine is not clinically relevant.

No formal drug-drug interaction studies have been conducted with CC-486. The impact of concomitant medications on the PK of CC-486 was assessed as part of the Phase 1/2 study in subjects with AML and MDS post HSCT using standard PK sampling during dose escalation on Day 1 of Cycles 1 and 2 (Study CC-486-AML-002). Following administration of CC-486 (200 mg once daily [QD]), azacitidine plasma concentration profiles and pharmacokinetic parameters were comparable when taken with or without concomitant medications. Concomitant medications included (but were not limited to) prophylactic antibiotics, calcineurin inhibitors, antifungals, and antiviral agents; anti-emetics and drugs to manage gastrointestinal complications; other concomitant treatments included RBC and platelet transfusions and myeloid growth factors. Although the protocol did not isolate drugs nor allowed for a proper wash-out of the co-medication in order to convincingly isolate effects, the results suggest a lack of significant drug–drug interactions with CC-486 and concomitant medications such as antibiotics, anti-emetics, or other drugs commonly administered in the post-transplant setting. Based on the know disposition characteristics of azacitidine, without influence of the major elimination and transporters enzyme systems, this type of behaviour is expected. Co-administration of carboplatin or nab-paclitaxel had minimal effect on CC 486 exposure, suggesting that Azacitidine has no influence in the renal elimination process and no direct effect on CYP2C8 (Study AZA-ST-001).

Pharmacokinetics using human biomaterials

N/A

2.4.3. Pharmacodynamics

Mechanism of action

Azacitidine exerts its antineoplastic effects through multiple mechanisms. Azacitidine is incorporated into DNA and RNA following cellular uptake and enzymatic biotransformation to nucleotide triphosphates. Azacitidine is similar to cytidine, which in turn is a building block of in the fundamental genetic material of cells (DNA and RNA). Azacitidine blocks the synthesis of DNA and RNA, and thus inhibits the growth of tumour cells. It also inhibits DNA methyltransferase and it is therefore believed to exert its antineoplastic effects also by causing hypomethylation (demethylation) of DNA as well as by direct cytotoxicity on abnormal bone marrow haematopoietic cells (see also Fandy et al. Cancer J, 2007, 13:40-48). As genetic and epigenetic changes co-operate in the pathobiology of AML and MDS, specifically, aberrant DNA hypermethylation in promoter regions of genes tends to silence gene expression, and therefore, reduced DNA methylation can lead to re-expression of genes altered in cancer cells. Deoxyribonucleic acid hypomethylation of these aberrantly methylated genes with azacitidine allows the re-expression of tumor suppressors, including genes involved in normal cell cycle regulation, cell differentiation and proliferation. Azacitidine also exerts antineoplastic effects by epigenetic regulation of the bone marrow microenvironment, including specific immune-mediated pathways associated with innate and adaptive immunity. In addition, azacitidine activates DNA damage and P53 response pathways

causing cell death and apoptosis of abnormal hematopoietic cells in the bone marrow. Azacitidine incorporates into RNA to decrease ribonucleotide reductase M2 subunit (RRM2) expression and attenuates RRM2 mRNA stability. Azacitidine inhibits RNA:m5C methyltransferases to limit RNA methylation, decreases protein synthesis, and induces cell cytotoxicity.

The rationale for the application of inhibition of DNA methylation, with substances like azacitidine, was the assumed reversion of hypermethylation induced tumour suppressor gene-inactivation. Since high-risk MDS shows a high prevalence of tumour suppressor gene hypermethylation azacitidine was suggested to be beneficial in MDS. By re-establishing cell cycle control by effective suppressor genes antiproliferative signals could be restored in affected cells. This mechanism could also contribute to restoring cell differentiation pathways. In fact, azacitidine was claimed to restore gene transcription in cell lines with hypermethylated genes and to induce a modest differentiation of transformed myeloid cell lines (Chim et al. Hematol Oncol, 2002, 20:167-176).

Whether the direct cytotoxic effects of azacitidine have any relationship with hypomethylation of DNA is yet unclear. In theory the alteration of suppressor gene activity could cause antiproliferative signals that negatively influence the normal cell cycle (also in normal haematopoietic cells) and thereby it could contribute to the myelotoxic adverse events.

Azacitidine is cytotoxic to a wide range of tumor cell lines, with increased sensitivity across leukemic cells in vitro. In wild-type mice, intraperitoneal administration of azacitidine using low exposure, extended dose schedules exhibited higher RNA and DNA incorporation of radiolabeled azacitidine into PBMC and bone marrow relative to higher exposure, limited duration schedules. In vivo, anti-leukemic activity of azacitidine was established through decreased tumor burden and increased survival in mouse leukemia models. Azacitidine causes death of rapidly dividing cells (Module 2; Section 2.6.6), including cancer cells that are no longer responsive to normal growth control mechanisms. Non-proliferating cells are relatively insensitive to azacitidine. Treatment with azacitidine can induce cellular differentiation by causing demethylation of genes silenced by hypermethylation. Azacitidine-induced demethylation and differentiation persists for many cell generations. In addition, hypermethylation of regions with dense CpG dinucleotides, referred to as CpG islands, spanning the promoter regions of tumor suppressor genes is commonly associated with cancers. The cause of aberrant hypermethylation of CpG islands is unclear, but de novo methylation has been shown to increase with age. Overexpression of DNA methyltransferases may also contribute to hypermethylation of CpG islands. Although the relative importance of DNA hypomethylation as a mechanism of azacitidine's antitumor activity against MDS and AML is not definitively established, recent trials have provided varied evidence relating clinical responses to azacitidine arising from its demethylating activity.

Primary and Secondary pharmacology

Primary pharmacology

The applicant has not conducted dedicated PD or PK/PD studies for this submission, but rather performed bridging PK, Efficacy and Safety studies with the oral administration of azacitidine.

The applicant has presented a literature review with references that highlight the well-known roles of azacitidine.

The primary pharmacodynamic properties of azacitidine are mediated through its incorporation into RNA and DNA, resulting in DNA hypomethylation as well as cytotoxicity in haematopoietic cells in the bone marrow of MDS and AML patients. Azacitidine exerts its antineoplastic effects through multiple mechanisms. Incorporation

of azacitidine into DNA results in the inactivation of DNA methyltransferases, reduction of DNA methylation, and alteration of gene expression, which can include re-expression of genes (including microRNAs) regulating tumor suppression, immune pathways, cell cycle, and cell differentiation.

The relationship between these mechanisms of action, and the extent to which each is contributing to clinical activity in humans is not yet fully understood. Recent clinical trials with azacitidine have documented its ability to induce DNA hypomethylation in patients after administration, but their results are not consistent.

The applicant has provided data from mainly 2 studies in which pharmacodynamic results were presented: Clinical Study AZA PH US 2007 CL 005 and Clinical Study AZA-ST-001 (Parts 1 and 2).

Study AZA PH US 2007 CL 005 was a Phase 1, dose-escalation study to evaluate the safety, PK, and PD of oral azacitidine in subjects with MDS, chronic myelomonocytic leukemia (CMML) or AML. The pharmacodynamic parameters evaluated in this study were the changes in global and gene-specific DNA methylation following azacitidine administration. Possible relationships between PD variables, PK parameters, and subject responses were also considered for exploration.

The study showed evidence of methylation reduction of highly methylated loci following SC and all oral azacitidine treatment schedules, with an exposure-response relationship (further addressed in the respective section). The greatest extent of hypomethylation at cycle end was provided by 21-day 300-mg QD or 200-mg BID dosing. A minimum biologically effective plasma exposure of approximately 100 ng·h /mL was defined based on DNA methylation change at Day 15.

Table 10: Changes in Global DNA Methylation Score (GDMS) with Subcutaneous Azacitidine and Oral Azacitidine in 7-day or Extended (14-day and 21-day) Dosing Schedules

Dosing schedule	Changes in Global DNA Methylation Score							
	Day 15 vs. Baseline		Day 22 vs. Baseline		Cycle End/Day 28 vs. Baseline		Day 22 vs. Day 15	
	Mean % difference	P value	Mean % difference	P value	Mean % difference	P value	Mean % difference	P value
SC azacitidine[a] 7-day QD (n=19)	-8.8%	<0.0001	-4.1%	0.0004	-3.2%	0.001	+4.3%	<0.0001
Oral azacitidine[b] 7-day QD (n=11)	-1.4%	0.27	+1.2%	0.264	+0.7%	0.433	+1.9%	0.109
Oral azacitidine 300 mg 14-day QD (n=18)	-3.3%	0.0151	-3.8%	0.001	-2.4%	0.0002	-0.71%	0.265
Oral azacitidine 300 mg 21-day QD (n=17)	-5.3%	0.0006	-6.7%	0.0001	-5.0%	0.0012	-1.42%	0.0068
Oral azacitidine 200 mg 14-day BID (n=3)	-5.9%	0.16	+2.6%	N/A[c]	-3.0%	0.23	NA[d]	NA
Oral azacitidine 200 mg 21-day BID (n=5)	-11.0%	<0.0001	-11.8%	0.0034	-9.1%	0.042	-0.73%	0.31

Abbreviations: BID = twice daily; QD = daily; NA = not assessed; SC = subcutaneous; vs. = versus.
[a] 75 mg/m^2/d
[b] Cycle 2, average for 300-mg, 360-mg, 480-mg, and 600-mg doses. Note that the "Baseline" value for oral azacitidine QDx7 days for cycle 2 was the GDMS value at the end of cycle 1 (after 1 cycle of SC AZA).
[c] N=1
[d] No samples taken on day 22.
n = the number of patients in a specific subject population; the actual sample size for each comparison may vary slightly due to missing data at various time points.

The Study AZA-ST-001 (Parts 1 and 2) evaluated azacitidine as a single agent and in combination with carboplatin or ABI-007 in subjects with relapsed or refractory solid tumors.

For the majority of subjects, a decrease in CpG methylation was observed following CC-486 treatment, with generally larger reductions observed in Arm C subjects and generally minor reductions observed in Arm A subjects.

Arm A treatment evaluated oral azacitidine in combination with CBDCA and all 13 subjects enrolled had evaluable PK. Arm B evaluated oral azacitidine in combination with nab-paclitaxel and had 24 PK evaluable subjects. Arm C evaluated oral azacitidine as a single agent and had 9 evaluable PK subjects.

In part 2 of the study, variable reductions in GDMS were observed at Day 15 in whole blood samples, with generally larger reductions observed in Arm A and Arm C subjects and generally minor reductions observed in Arm B subjects. Reduction in GDMS was observed in tumor tissue from 1 NPC subject in Arm C at Day 15.

Secondary pharmacology

As an agent that incorporates into nucleic acids and alters gene expression, azacitidine also has the potential to cause harm. In addition to its role in inhibition of DNA methylation and induction of cell differentiation, azacitidine has immunosuppressive, antimicrobial, genotoxic, embryotoxic, teratogenic, and carcinogenic effects. These secondary effects are in line with the pharmacologic activity of other pyrimidine analogues used as antiviral and antineoplastic agents.Also, azacitidine has the ability to express viral genes and antigens.

Studies also demonstrate that azacitidine can reactivate latent viruses such as Epstein Barr Virus (EBV) in vitro (tissue culture), and can induce EBV antigen production in EBV+ patients. Evidence for a direct relationship

between azacitidine treatment and viral infections including re-expression or assembly of the entire EBV genome (or virions) or an increase in lytic stages of viral replication cannot be established. . In addition, viral reactivation is currently being and will be monitored by the Applicant through routine risk evaluation in the periodic safety update report (PSUR) for azacitidine, under the safety concern of infection in agreement with prior Pharmacovigilance Risk Assessment Committee (PRAC) recommendation.

A dedicated QT study has not been conducted for CC-486 considering no clinically significant QTc prolongation has been observed with the injectable form (IV or SC) of azacitidine. In addition, the C_{max} and AUC of azacitidine after 300 mg oral administration was approximately 75% lower than when given SC at 75 mg/m^2, demonstrating lower daily systemic exposures of azacitidine when given orally at clinically relevant doses compared to SC administration (AZA PH US 2008 CL008).

Pharmacodynamic interactions with other medicinal products or substances

No formal drug-drug interaction (DDI) studies have been performed with CC-486. Although some data has been presented for PK interactions, no PD interactions were mentioned in the clinical overview, clinical summary or clinical study reports.

However, on the non-clinical summary some information was provided regarding potential pharmacodynamic interactions.

Concurrent administration of azacitidine with other antineoplastic agents may affect the pharmacodynamics of either compound. The interaction of azacitidine with other commonly used antineoplastic agents is frequently dependent on the dose, sequence, and schedule of administration. The degree of tumor cell cytotoxicity with combination therapy may be antagonistic, additive, or synergistic. The pharmacodynamic interactions between azacitidine and other antineoplastic agents are presented in the Table 18 below.

Table 11: Interaction of Azacitidine with Other Anti-Neoplastic Agents

Agent	Test System	Effect of Azacitidine
Topoisomerase inhibitors	Chinese hamster ovary cells (Lopez-Baena, 1998)	Enhanced sensitivity to topoisomerase inhibitors
Adozelesin	Chinese hamster ovary cells (Smith, 1995)	Enhanced synergistic cytotoxicity
Cadmium	TRL 1215 rat liver cells (Waalkes, 1985)	Increased tolerance to cadmium cytotoxicity through enhanced expression of metallothionein gene
Vincristine	L1210 leukemia in vivo (Presant, 1981)	Cytotoxicity was variable depending on agent sequence
β-cytosine arabinoside	L1210 leukemia in vivo (Presant, 1981)	Cytotoxicity was antagonistic if given simultaneously, additive if given sequentially
Adriamycin	L1210 leukemia in vivo (Presant, 1981)	Cytotoxicity was antagonistic if given simultaneously, additive if given sequentially
Pyrazofurin	Murine P388 and L1210; Colon carcinoma 26 (Chiuten, 1979)	Increased cytotoxicity and efficacy when used after pyrazofurin

Agent	Test System	Effect of Azacitidine
Pyrazofurin	L5178Y and human leukemia cells (Cadman, 1978)	Administration of pyrazofurin prior to azacitidine increased both the accumulation of azacitidine and the killing of leukemia cells
Curcumin	Leukemic cell lines (U-937, HL-60, K-562, and OCI-AML3) and patient bone marrow and healthy donors in vitro (Martín, 2019)	Synergy between azacitidine and curcumin; decreased proliferation and an increase in apoptosis. Combination showed low cytotoxicity in healthy samples
ATRA	Glioma xenograft models, human SLGC line NCH644 in vivo (Schmoch, 2016)	Combined with ATRA increased aggressiveness of glioma xenograft tumors
Cytarabine, Etoposide	AML cells (U937 and HL60) and non-small cell lung cancer cells (A549 and HTB56) in vitro (Fuller, 2015)	Synergistic cytotoxicity in AML and NSCLC
ONC201 (selective antagonist the G protein–coupled receptor DRD2, DRD3)	HL-60, MOLM-14, MV4;11 AML cells in vitro (Prabhu, 2018)	Azacitidine combines synergistically with ONC201 in AML in vitro
Retinoid acid and glucocorticoids	Lung cancer in vivo models; combinations with azacitidine and/or SAHA (Romero, 2017)	Sensitization of retinoids and glucorticoids with combination of azacitidine and SAHA in MYC-activated lung cancers
Lenalidomide	In vitro and ex vivo assays (Govindaraj, 2014)	Combination effect enhanced with azacitidine, by reducing TNFR2 expression and augmenting effector cytokine production (IFNr and IL-2) by CD4 T cells
Venetoclax (ABT-199)	(Chen, 2019); AML cell line in vitro (Bogenberger, 2014)	In vitro sensitization of AML cell lines
Butyrate (HDAC inhibitor)	MCF10A4, CAL51, and 4T1 cells tumor spheres; mouse 4T1 breast tumor model in vivo; (Pathania, 2016)	Treatment with DNMT and HDAC inhibitors restricts CSCs; azacitidine and butyrate treatment significantly increased the overall survival of tumor bearing mice
Pevonedistat (TAK-924/MLN4924) (inhibitor of NEDD8-activating enzyme)	HL-60 AML model in vivo (Smith, 2011)	Azacitidine plus MLN4924 combinations induced complete and sustained tumor regressions
Entinostat (MS275); HDACi	Mouse ovarian model ID8-VEGF-Defensin cells implanted in C57BL/6NHsd (C57BL/6) mice (Stone, 2017)	Enhanced combinatorial efficacy of azacitidine with entinostat.

Agent	Test System	Effect of Azacitidine
Entinostat (MS275); HDACi	AML and ALL cells in vitro (Gao, 2008)	Combination increases cytotoxic effects of tumor cells, by intracellular potentiation of reactive oxygen species.
Entinostat (HDAC inhibitor)	Ovarian cancer cell lines in vitro; PDX, ID8 tumor model in vivo (Turner, 2017)	Combination treatment showed higher MHC II protein expression compared to single agents. In patient derived xenografts, CIITA, CD74, and MHC II mRNA transcripts were significantly increased after combination treatment. Combination treatment significantly reduced ID8 tumor growth
Givinostat (ITF2357) HDACi	Mouse ovarian model ID8-VEGF-Defensin cells implanted in C57BL/6NHsd (C57BL/6) mice (Stone, 2017)	Enhanced combinatorial efficacy of azacitidine with givinostat.
HDAC inhibitors (Givinostat/ITF-2357, Mocetinostat/MGCD-0103, and Entinostat/MS-275)	Non-small lung cancer (NSCLC) cell lines in vitro; LSL-KrasG12D mouse model of NSCLC (Topper, 2017)	Potent augmentation of antiproliferative effect in combination in vitro cell line panel; Combination of azacitidine and ITF-2357 reduces lung tumor burden in LSL-KrasG12D mice.
Panobinostat (HDAC inhibitor)	Human AML cell lines in vitro and MV4;11 AML tumor model (Gopalakrishnapillai, 2017)	Combination treatment synergistically augmented AML cell death in vitro and induced remission in mouse xenograft models of AML
Panobinostat (HDAC inhibitor), cytarabine	Acute lymphoid leukemia cells in vitro and ex vivo (Quagliano, 2017)	Azacitidine and panobinostat show synergy in combination and overcome the chemoprotection induced by osteoblasts better than cytarabine and single agent treatments
ACY-957 (HDAC inhibitor)	AML cell lines and Molm-13 in vivo model (Min, 2017)	ACY-957 synergizes with azacitidine in vitro and enhances in vivo anti-leukemic activity
Enasidenib (IDH2 inhibitor)	Genetic mouse AML models of IDH2 R140Q FLT3 ITD; in vivo (Shih, 2017)	Enhanced anti-leukemic response to combination therapy
Enasidenib (IDH2 inhibitor)	Normal B-lymphoblast peripheral blood cell line and AML cell lines in vitro (Tong, 2019)	Azacitidine uptake was more than 2-fold higher in AML cells than in normal B-lymphoblast cell line. Enasidenib inhibited azacitidine uptake into OCI-AML2, TF-1 and PBC cells in a concentration-dependent manner.
Quizartinib (FLT3 inhibitor)	Genetic mouse AML models of Tet2−/− Flt3ITD; in vivo (Shih, 2017)	Enhanced anti-leukemic response to combination therapy

Agent	Test System	Effect of Azacitidine
Quizartinib (FLT3 inhibitor)	AML cell lines and primary cells in vitro (Chang, 2016)	Simultaneously treatment leads to the highest degree of anti-leukemic activity, observed as inhibition of cell growth and induction of apoptosis and differentiation.
Gilteritinib (FLT3 inhibitor)	FLT3-ITD AML model MV4;11 and Molm-13 in vivo (Ueno, 2019)	Azacitidine and gilteritinib combined treatment reduced tumor volumes to a greater extent than single agents.
ABBV-075 (BET inhibitor)	SKM-1 AML tumor model in vivo (Bui, 2017)	ABBV-075 enhanced the efficacy of azacitidine
OTX015 (BET inhibitor)	Kasumi AML cell line in vitro (Coude, 2015)	Sequential combinations of OTX015 with azacitidine have a synergistic effect
LDE225 (erismodegib (SMO inhibitors)	AML cell lines in vitro (Tibes, 2015)	Combinations demonstrated synergistic activity using combination index analyses in AML cell lines
Volsertib (PLK1 inhibitor)	MV-4-11 tumor model in vivo (Rudolph, 2015)	Combination therapy with volasertib showed improved efficacy compared to single agents
Erlotinib (EGFR inhibitor)	SKM1 AML cells in vitro (Lainey, 2013)	Combination induced synergistic effects by blocking cell-cycle progression and induction of caspase-dependent apoptosis
Ruxolitinib (JAK inhibitor)	EOC cells with azacitidine and ruxolitinib in vitro (Chiappinelli, 2015)	Azacitidine activation of type I, IFNb-mediated signaling through JAK/STAT, JAK inhibitor ruxolitinib strongly reduced interferon stimulated genes (ISG) responses.
Tagraxofusp; CD123-targeted therapy consisting of interleukin-3 fused to a truncated diphtheria toxin payload	THP-1 cells and resistant cells (Togami, 2019)	Azacitidine restored diphthamide synthesis pathway enzyme (DPH1) expression and tagraxofusp sensitivity in resistant cells
Lintuzumab (SGN-33)	In vitro assays and HL60cy AML model in vivo (Sutherland, 2010)	Azacitidine significantly enhances the in vivo activity of lintuzumab (SGN-33). Azacitidine significantly enhanced lintuzumab activity by enhancing tumor cell killing through antibody-dependent cellular cytotoxicity (ADCC) and phagocytic (ADCP) mechanisms.
Gemtuzumab ozogamicin; anti-CD33 monoclonal antibody	AML cell lines in vitro (Balaian, 2006)	Azacitidine treatment of primary AML cells increases response to anti-CD33 mAb and GO

Agent	Test System	Effect of Azacitidine
Lintuzumab (SGN-33)	In vitro assays and HL60cy AML model in vivo (Sutherland, 2010)	Azacitidine significantly enhances the in vivo activity of lintuzumab (SGN-33). Azacitidine significantly enhanced lintuzumab activity by enhancing tumor cell killing through antibody-dependent cellular cytotoxicity (ADCC) and phagocytic (ADCP) mechanisms.
Anti-CTLA4 antibody	Mouse B16-F10 melanoma model in vivo (Chiappinelli, 2015)	Azacitidine potentiates anti-CTLA-4 antibody immune checkpoint therapy
Anti-PD-1 antibody	Mouse ovarian model ID8-VEGF-Defensin cells implanted in C57BL/6NHsd (C57BL/6) mice (Stone, 2017)	Combination treatment induces immune activation pathways, and enhances the modulation of the immune microenvironment, increasing T and NK cell activation and reducing macrophages to increase the survival of the tumor bearing mice.
Anti-PD-1, anti-CTLA4 and entinostat (HDAC Inhibitor)	Mouse CT26 colon and 4T1 breast tumor models in vivo (Kim, 2014)	Azacitidine cotreatment with HDAC inhibitor and checkpoint inhibitors markedly improved treatment outcomes

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

The PK of azacitidine has been previously characterized (initially investigated in the 1970s following treatment of patients with the radiolabelled drug and clinical results published during the period 1989 to 2002) following both IV and SC administration and demonstrated rapid and nearly complete absorption of azacitidine following SC administration (T_{max} occurred within 30 minutes and a bioavailability of 89% relative to IV administration), and rapid elimination after both methods of administration (t1/2 of 0.69 and 0.36 hours for SC and IV administration, respectively).

Based on the data provided for oral azacitidine, it can be concluded that azacitidine undergoes rapid and possibly complete biotransformation by spontaneous chemical degradation as well as metabolism. The metabolism appears not to be mediated by CYPs, UGTs, SULTs or GSTs, and it is suggested that metabolism proceeds via the cytosolic enzyme cytidine deaminase.

Absorption of azacitidine is not affected by changes in gastric pH; no dose modification is required when co-administered with a PPI or other pH modulators. Onureg can be administered with or without food (Study CC-486-CAGEN-001).

The small amount recovered in the urine indicates (2% of the dose administered orally, with an estimated absolute bioavailability of ca. 11%) that non-renal elimination (e.g., metabolism, hydrolysis, and/or degradation) is the predominant pathway for parent azacitidine clearance.

Azacitidine appears to have a high clearance, a short half-life drug with low oral bioavailability.

In summary, azacitidine pharmacokinetics following oral (as opposed to IV or SC administration, which are well established), has been scarcely studied in this dossier. The absence of a formal mass balance study precludes firm conclusions on the fate of the drug during absorption. However, given that it is demonstrated that azacitidine undergoes almost complete non-enzymatic hydrolysis, there is no basis to require a new mass balance study after oral administration in humans. No *in vivo* metabolism or metabolites PK have been studied. A PopPK study supported the main conclusions on special populations and drug/drug interactions.

Special populations

Renal impairment

Despite increased azacitidine exposure by approximately 70% after single and 41% after multiple subcutaneous administrations in six subjects with severe renal impairment, this increase in exposure was not correlated with an increase in adverse events and dose modification was not recommended in subjects with renal impairment

Moreover, creatinine clearance was identified as a significant covariate on CL/F of oral azacitidine in the final PopPK model. However, due to the low oral bioavailability of azacitidine, no dose adjustment is recommended in renally-impaired subjects treated with 300 mg oral azacitidine.

Impaired hepatic function

No formal studies have been conducted in patients with hepatic impairment. Hepatic impairment is unlikely to affect the PK to a clinically relevant extent since azacitidine undergoes spontaneous hydrolysis and deamination mediated by cytidine deaminase. A population PK analysis determined that AST (8 to 155 U/L), ALT (5 to 185 U/L) and mild hepatic impairment (BIL ≤ ULN and AST > ULN, or BIL 1 to 1.5 × ULN and any AST) did not have clinically meaningful effects on the PK of azacitidine. The effects of moderate to severe hepatic impairment (BIL > 1.5 × ULN and any AST) on the PK of azacitidine is unknown.

Age, Body Weight, Gender and Race

As a limited number of non-white subjects were available for PopPK analysis, race covariate analysis results should be interpreted with caution. Only 2.3% of subjects in PopPK analysis were of Asian descent, and results from studies exploring the PK in and Asian-Pacific Island subjects were inconclusive due to high variability and small number of subjects enrolled. The SmPC includes a statement in Section 5.2 that the effects of race/ethnicity on the pharmacokinetics of oral azacitidine is unknown.In general, gender, age (46 to 93 years), race (92% white), body mass index (BMI [15.7 to 51.7 kg/m^2]) and body weight (39.3 to 129 kg) have shown not to be clinically significant covariates influencing azacitidine exposure.

Interactions

Appropriate conclusions have been drawn from the performed in vitro and in vivo studies. Azacitidine is not a substrate, inhibitor or inducer of CYP enzymes and transporters. Therefore, no potential for inhibition or inducing effect on these systems exists. Two in vivo studies support the non-existing interaction with concomitant medications such as antibiotics, antiemetics, or other drugs commonly administered in the post-transplant setting. Moreover, co-administration of carboplatin or nab-paclitaxel had minimal effect on oral azacitidine exposure.

<u>Pharmacodynamics</u>

The applicant has provided a mixed clinical pharmacodynamics package, with literature references and clinical studies. The clinical pharmacodynamics summary was focused on the pharmacokinetic characterization of the oral administration of azacitidine, which was indeed the main difference regarding the already approved medicine with injectable azacitidine. Azacitidine is a DNA methyltransferase inhibitor and epigenetic modifier. Azacitidine is incorporated into DNA and RNA following cellular uptake and enzymatic biotransformation to nucleotide triphosphates. Incorporation of azacitidine into the DNA of AML cells, modified epigenetic pathways through the inhibition of DNA methyltransferases, and reduction of DNA methylation. This led to alteration of gene expression, including re-expression of genes regulating tumour suppression, immune pathways, cell cycle, and cell differentiation. Incorporation of azacitidine into the RNA of AML cells, inhibited RNA methyltransferase, reduced RNA methylation, decreased RNA stability, and decreased protein synthesis.

The applicant has presented data from studies in which pharmacodynamic parameters were evaluated. However, the clinical guidelines for diagnosis and follow-up of acute myeloid leukemia present as one of the pivotal measurements the percentage of blasts. Other than the studies in which efficacy endpoints (OS and RFS) were being evaluated, the PD endpoints studied were mainly related to measurement of methylation. Although it is recognized that cell methylation is an endpoint directly related to the mechanism of action, there are more clinically relevant endpoints also directly related to the pharmacodynamic effects of azacitidine.

Facing the possibility of the use of other endpoints (besides DNA methylation) as biomarkers for efficacy and pharmacodynamic effect, like blasts count/percentage the applicant has correlated MRD results as an exploratory measure of disease burden (related to residual bone marrow leukemic cells post therapy) which served as a deeper and more compelling PD readout of CC-486 efficacy. The correlation performed by the applicant is valid and served as a PD endpoint in the summarized study.

Although in the context of the current application, azacitidine is intended to be administered as monotherapy, there will be situations in which azacitidine might be clinically useful in concomitant administrations with other antineoplastic agents. As such, the applicant was asked to include a text in section 4.5 of the SmPC addressing the main possible clinical issues in case of a coadministration setting with other antineoplastic agents (in case of concomitant administration with other antineoplastic agents, caution and monitoring is recommended as an antagonistic, additive, or synergistic pharmacodynamic effect cannot be excluded. These effects may be dependent on the dose, sequence and schedule of administration).

2.4.5. Conclusions on clinical pharmacology

Azacitidine has an extensive history as an antineoplastic agent and research tool over the past 4 decades. The pharmacology data presented in this application were derived from numerous research publications rather than from GLP-compliant studies designed specifically to support an application for marketing authorisation.

Azacitidine is believed to exert its antineoplastic effects through multiple mechanisms. Azacitidine is incorporated into DNA and RNA following cellular uptake and enzymatic biotransformation to nucleotide triphosphates.

All the issues initially raised related to pharmacodynamics and pharmacokinetics of oral azacitidine were in general adequately clarified.

The relevant information has been included in the SmPC sections 4.2 and 5.2.

2.5. Clinical efficacy

2.5.1. Dose response study

A dedicated dose response study with the to-be-marketed oral formulation of azacitidine tablets has not been submitted.

The dose and schedule of oral azacitidine administered as 300 mg QD for the first 14 days of every 28-day treatment cycle selected for evaluation in the pivotal study Study CC-486-AML-001 were based on cumulative safety, efficacy, tolerability, and biologic data observed in Phase 1 Study (AZA PH US 2007 CL 005).

Study AZA PH US 2007 CL 005 was designed to determine the maximum tolerated dose of oral azacitidine administered according to different treatment schedules and to evaluate the PK behaviour of azacitidine administered by both oral and SC routes.

The study AZA PH US 2007 CL 005 was conducted in 2 parts:

- Part 1 was designed to compare the PK and PD of SC azacitidine administered for 7 days of a 28-day cycle in Cycle 1 (75 mg/m²/day) to that of oral azacitidine administered for 7 days of a 28-day cycle starting in Cycle 2 Day 1. For Cycle 2 and beyond, each subject received oral azacitidine QD for the first 7 days of each 28-day cycle. The starting dose of oral azacitidine in Cycle 2 was 120 mg/day.

- Part 2 was designed to evaluate oral azacitidinde during extended treatment periods (14 and 21 days) with both QD and BID treatment schedules in each 28-day cycle. Part 2 began once the MTD in Part 1 was determined and the MTD expansion cohort for that schedule had fully enrolled. During Cycles 1 and beyond of Part 2, subjects received oral azacitidine QD or BID for the first 14 or 21 days of each 28-day cycle. The 14-day QD treatment regimen was evaluated first with a starting dose of 300 mg.

Part 1 and Part 2 were each followed by an open-label extension phase to allow subjects to continue to receive oral azacitidine.

With dose increases from 120 to 600 mg, exposure increased in a dose related manner. In Part 1 of the study, the mean terminal half-life was approximately 1.7 hours for SC azacitidine and ranged from 0.4 to 1.0 hour for oral azacitidine. The mean relative azacitidine oral bioavailability ranged from 6.9% to 22% across dose levels compared with SC treatment. In Part 2, similar PK results to Part 1 were observed. Pharmacokinetic parameters obtained following single 200-mg and 300-mg administrations (Day 1) and multiple 200-mg BID and 300-mg QD administrations (Day 14 and Day 21) were overall similar, indicating no accumulation.

Following SC and oral administration, azacitidine was rapidly absorbed, with a median Tmax ranging from 0.5 to 1.5 hours postdose. Mean terminal half-life was approximately 1.7 hours for SC azacitidine and ranged from 0.4 to 1.0 hour for oral azacitidine.

The proposed 300 mg QD for 14 days regimen was determined to be biologically active (maintaining hypomethylation until the end of the 28-day treatment cycle [Garcia-Manero, 2016]) and was associated with an overall response rate (CR, CRi, PR, or any transfusion independence) in approximately 32% of subjects treated. This regimen was also generally well-tolerated, and therefore, could allow subjects to remain on study for protracted periods of time.

2.5.2. Main study

Study CC-486-AML-001:

Phase 3, double-blind, randomized, placebo-controlled, multicenter study designed to compare the efficacy and safety of CC-486 plus BSC to placebo plus BSC as maintenance therapy in subjects who achieved CR/CRi after induction with intensive chemotherapy with or without consolidation.

Methods

Study Participants

The study population represented AML subjects with limited treatment options, as all subjects were not considered candidates for allogeneic bone marrow or stem cell transplant by the Investigator (including those who were not eligible, did not have a transplant donor available, or chose not to proceed to HSCT). All subjects were required to receive intensive chemotherapy to achieve CR/CRi before entry into the study; however, specific regimens of induction and consolidation chemotherapy were not mandated in the protocol.

To avoid enriching the study population with patients with better prognoses, subjects were required to be randomized within 4 months (± 7 days) of achieving CR/CRi, as longer durations of remissions have been associated with better outcomes in patients with AML (Breems, 2005). Further, this window of up to 4 months allowed time for eligible patients to receive up to 4 cycles of consolidation chemotherapy. Subjects were randomized in a 1:1 ratio to receive CC-486 at a starting dose of 300 mg QD for 14 days of a 28-day cycle or placebo. The study was conducted with the ethical principles of Good Clinical Practice (GCP), according to the International Council for Harmonisation (ICH) Harmonised Tripartite Guideline.

Main inclusion criteria

- Male or female subjects ≥ 55 years of age at the time of signing the ICF;

- Newly diagnosed, histologically confirmed de novo AML or AML secondary to prior myelodysplastic disease or CMML;

- Received induction therapy with intensive chemotherapy with or without consolidation therapy;

- Achieved first CR/CRi status within 4 months (± 7 days) prior to randomization

Main exclusion criteria

- Had suspected or proven acute promyelocytic leukemia (FAB M3) based on morphology, immunophenotype, molecular assay, or karyotype; or AML with previous hematologic disorder such as chronic myeloid leukemia or myeloproliferative neoplasms, excluding MDS and CMML;

- Had AML associated with inv(16), t(8;21), t(16;16), t(15;17), or t(9;22) karyotypes or molecular evidence of such translocations;

- Had prior bone marrow or stem cell transplantation;

- Achieved CR/CRi following therapy with hypomethylating agents;

- Received therapy with hypomethylating agents for MDS and subsequently developed AML within 4 months of discontinuing the therapy with HMAs;

- Had proven central nervous system leukemia;

- Was a candidate for allogeneic bone marrow or stem cell transplant at screening;

Treatments

Following screening, eligible subjects were randomized to receive 300 mg Onureg or matching placebo QD for the first 14 days of each 28-day treatment cycle. One cycle of study treatment was dispensed to each subject on Day 1 of each treatment cycle.

The first dose was to be administered within 3 days after randomization and within 4 months (± 7 days) of achieving CR/CRi.

Subjects with AML relapse (≥ 5% and ≤ 15% blasts in the bone marrow) had the option to continue treatment with an extended dose schedule to 300 mg QD for 21 days, provided it was in the best interest of the subject to do so as judged by the Investigator. Similarly, if subjects experienced toxicity considered possibly related to treatment, dosing with investigational product could be interrupted or delayed, reduced to 200 mg daily for 14 days or 200 mg daily for 7 days in a stepwise fashion.

Objectives

The primary objective of the study was to:

- Determine whether maintenance therapy with Onureg improved Overall Survival (OS) compared with placebo in the study population

The secondary objective:

- Included effect of Onureg on RFS (Relapse-free Survival), safety and tolerability, HRQoL and healthcare resource utilization

Outcomes/endpoints

The primary endpoint was Overall Survival (OS), defined as the time from randomization until death from any cause.

The key secondary endpoint was Relapsed Free Survival (RFS), defined as the time from randomization to the date of first documented relapse or death from any cause, whichever occurred first.

Other secondary endpoints were: Time to relapse from CR/Cri; Time to discontinuation from treatment and Safety/tolerability.

Sample size

For the determination of the sample size, the equality of OS curves was compared between the oral azacitidine and placebo treatment arms using a stratified log-rank test. Assuming a median OS of 16 months in the placebo

treated group (Baer, 2010; Baer, 2011), a median OS of 22.9 months in the oral azacitidine treated group (43% improvement), and a study duration of 60 months with a drop-out rate of 5% from both treatment arms, over the duration of the study, this design required 330 deaths and approximately 460 subjects (230 per treatment arm) to be randomized in order to achieve at least 90% power to detect a constant hazard ratio of 0.70 and demonstrate a statistically significant difference in OS. It is assumed that the OS distribution is exponential with a constant failure (hazard) rate and that accrual is non-uniform during an accrual period of 36 months with 25% of the subjects accrued during each of the first 2 years of enrolment (50% accrued at 24 months) and the remaining 50% accrued during the last year of enrolment. Sample size calculations are based on a one-sided alpha of 0.025 with one interim analysis for futility after 30% of the events have occurred.

Randomisation

Subjects were randomized in a 1:1 ratio to receive 300 mg Onureg QD or placebo. Treatment was assigned by a central randomization procedure using an Interactive Voice Response System (IVRS).

Blinding (masking)

This was a double-blind study.

Statistical methods

The below Table 19 provides a summary of statistical methods used for evaluation of efficacy in Study CC-486-AML-001.

Table 12: Endpoints and Statistical Methods for Evaluation of Efficacy in Study CC-486-AML-001

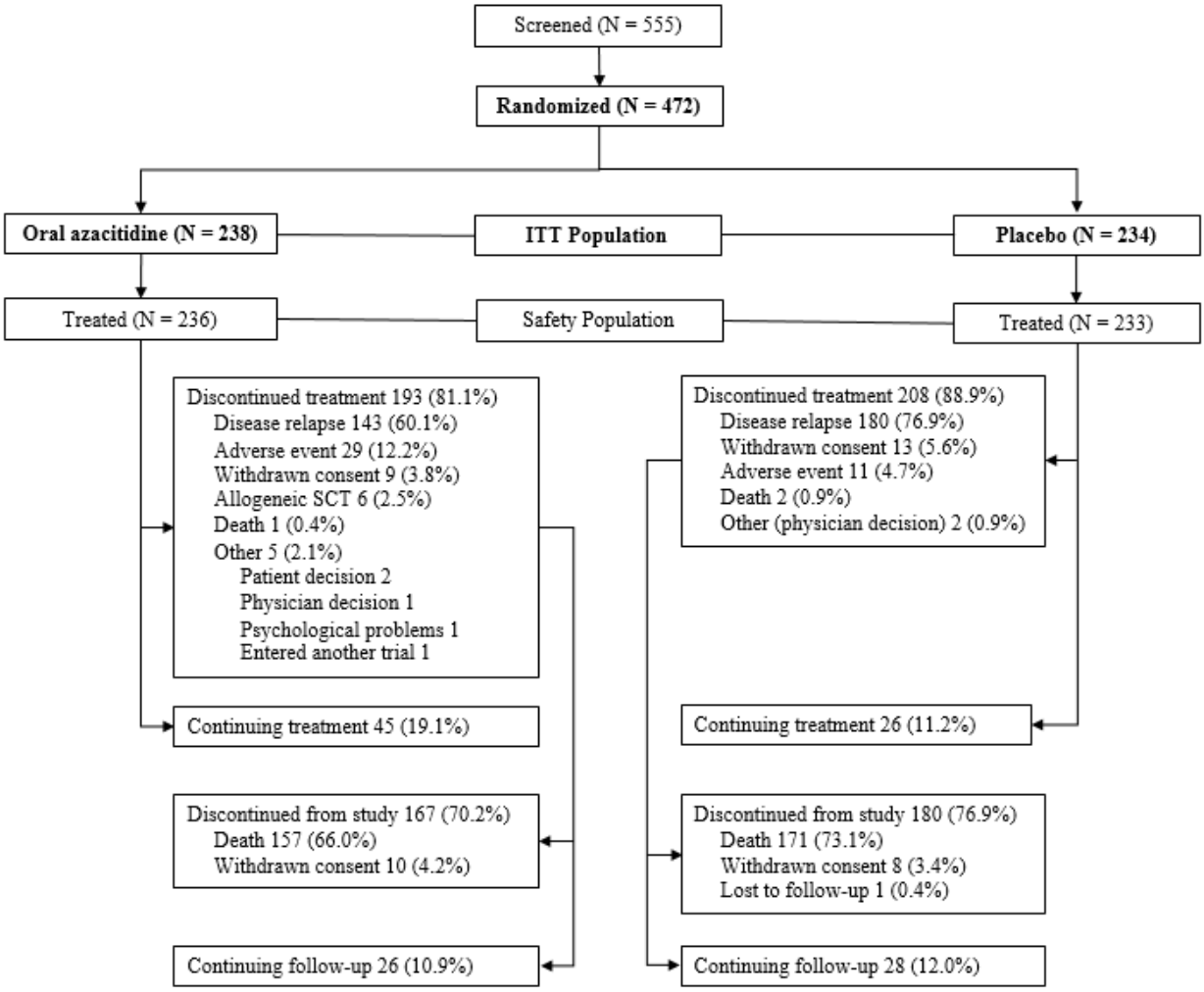
Endpoint	Definition Details	Statistical Methods
Primary		
OS	Time from randomization to death from any cause Defined as the number of days from the date of randomization until the date of death from any cause and calculated as (date of death - date of randomization + 1). • Last date known alive was derived by searching through all valid assessment dates in all study datasets to identify the last valid assessment date available for each subject • Censored at date last known to be alive if alive at end of follow-up period or lost to follow-up. • Censored at date of withdrawn consent tor subjects who withdrew consent	Based on ITT population Stratified log-rank test based on randomization strata provided confirmatory p-value; p-value from unstratified log-rank test was also provided as supportive analysis. Kaplan-Meier method was used to estimate the survival distribution functions for each treatment group. Displays by treatment group included: • KM estimates for median OS • Q1, Q3 • 2-sided 95% CIs • KM survival curves The numerical difference and 95% CI of the difference in the median, Q1, and Q3 between the treatment groups were presented. Stratified Cox proportional hazards model was used to estimate the HR (95% CIs) for CC-486 relative to placebo. Sensitivity analyses (see SAP Section 11.2.2 in CSR CC-486-AML-001 Appendix 16.1.9): • mITT • Censoring for withdrawn consent • Censoring for use of any subsequent AML therapy (including post-treatment transplant) • Censoring for use of disease-modifying subsequent AML therapy (defined as any subsequent AML therapy that is not hydroxycarbamide, as it is unlikely to lead to a significant effect in prolonging survival) • Censoring for post-treatment transplant • Cox proportional hazard model with covariates adjustment • Inverse probability of censoring weighted method • Regression-based imputation analysis method (Luo, 2015) • Time-dependent Cox model with interaction of treatment and time, including figure of hazard function over time • Restricted mean survival time • Piecewise Cox regression • Generalized Wilcoxon test

Endpoint	Definition Details	Statistical Methods
Key Secondary		
RFS	Time from date of randomization to the date of documented relapse or death from any cause, whichever occurred first. Censored per FDA guidance (see SAP Table 2 in CSR CC-486-AML-001 Appendix 16.1.9) Documented relapse was defined as the earliest date of: • ≥ 5% bone marrow blasts from the central pathology report • appearance of blasts in the peripheral blood with confirmation of bone marrow blasts ≥ 5% within 100 days (ie, approximately 3 cycles), or • at least 2 peripheral blood blasts ≥ 5% within 30 days	Based on the ITT population Methods are as described for the primary endpoint To preserve the overall alpha level at 0.05 across the OS and RFS endpoints, formal statistical inference for the RFS analyses was made only if superiority of CC-486 was demonstrated for the primary efficacy endpoint, OS, at the 2-sided 0.05 significance level. Sensitivity analyses: • mITT • Documented relapse based on Investigator-assessed response • Censoring rules based on EMA guidance (see SAP Table 3 in CSR CC-486-AML-001 Appendix 16.1.9)
Additional Secondary		
Time to relapse	Defined as the time from the date of randomization to the date of documented relapse.	Based on the ITT population Analyzed using a competing risk analysis where death without documented relapse was treated as a competing risk for relapse. Censoring rules were similar to those described under RFS. The cumulative incidence function (Kalbfleisch, 1980) for time to relapse was summarized and displayed graphically for each treatment group. Kaplan-Meier methods were used to estimate time-to-event curves.
Time to treatment discontinuation	Defined as the time from the date of randomization to the date of discontinuation from investigational product. Censored at date of last visit if ongoing in treatment at the time of study closure.	Based on the ITT population Analyzed using a competing risk model with reason for treatment discontinuation classified as: • Disease relapse • Adverse event(s) • Became eligible for bone marrow or stem cell transplant • Withdrawal of consent/lost to follow-up/protocol violation/ Other • Death Cumulative incidence curves were estimated and summarized for each specific reason for discontinuation from treatment by treatment group

For the main analysis, three different populations were defined: the Intent-to-Treat Population (ITT), the Modified intent-to-treat population (mITT) and the Safety Population.

Results

Participant flow



Recruitment

A total of 555 subjects were screened for participation in the study and 472 were randomized (238 to oral azacitidine and 234 to placebo), at 147 investigational sites across Europe (66.5%), North America (16.7%), Australia (10.4%), Asia (4.9%), and South America (1.5%).

Conduct of the study

Protocol deviations/violations were identified and reported by site and assessed by the clinical research physician or designee following company standard operational procedure.

Table 13: Summary of Protocol Amendments (CC-486-AML-001)

Amendment Number Date of Amendment	Section(s)	Change and Rationale
1.0 29 Dec 2015	Inclusion Criterion #2 Protocol Summary, Sections 4.1, 6.3, 7.1, 7.2, 7.2, 8.3, and 10.6.2.3	Modified to allow patients with AML secondary to CMML to enroll in the study, as CMML shares clinical and biological features with MDS and accounts for approximately 10% of all cases of MDS.
	Inclusion Criterion #4 Throughout document	Modified to amend the amount of time required for subjects to be in CR or CRi from 3 months to 4 months (± 7 days) based on Investigators' suggestions and differences in global treatment practices.
	Protocol Summary, Section 4.1, Figure 1, Table 1, Section 6.7	Based on recommendations from Investigators, bone marrow aspirate or biopsy sampling during the double-blind Treatment Phase was changed from Day 1 (± 3 days) of every third cycle, such that after 24 cycles, bone marrow aspirate could be collected at Cycles 30 and 36 and as clinically indicated beyond Cycle 36 at the discretion of the Investigator.
	Table 1 (Table of Events)	Reduced the number of clinical visits in a cycle from 2 (Days 1 and 15) to 1. Beginning with Cycle 25, the Day 15 Visit was optional and could occur if clinically indicated at the discretion of the Investigator.
	Protocol Summary, Sections 2.3 and 3.3	Added an exploratory objective to determine the plasma concentration of azacitidine and to explore exposure-response relationships of efficacy and safety endpoints to reflect PK analyses already being performed.

Amendment Number Date of Amendment	Section(s)	Change and Rationale
2.0 08 Nov 2018	Protocol Summary, Sections 4.1, and Appendix K	Addition of an extension phase (EP) to allow all subjects on treatment with CC-486 and demonstrating clinical benefit to continue to do so. In addition, all subjects who were discontinued from the Treatment Phase (irrespective of randomization arm) and continuing in the Follow-up Phase, were followed for survival for at least another 12 months, until death, withdrawal of consent, study closure, or lost to follow-up.
	Section 4.1, Section 4.3, Section 14.8	Language was added to close the study when either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary and/or secondary analysis, whichever was the later date.
	Section 11.6	On recommendations from Health Regulatory Authorities, deleted "Adverse events such as disease progression, death related to disease progression (in the absence of serious IP-related events) and serious events due to the relapse of the studied indication will not be subject to expedited reporting by the Sponsor to regulatory authorities…".

Baseline data

Table 14: Baseline Disease Characteristics (Intent-to-Treat Population)

Parameter	CC-486 (N = 238)	Placebo (N = 234)	Total (N = 472)
Initial AML classification - n (%)			
AML with recurrent genetic abnormalities	39 (16.4)	46 (19.7)	85 (18.0)
AML with myelodysplasia - related changes	49 (20.6)	42 (17.9)	91 (19.3)
Therapy-related myeloid neoplasms	2 (0.8)	0	2 (0.4)
AML not otherwise specified	148 (62.2)	145 (62.0)	293 (62.1)
Missing	0	1 (0.4)	1 (0.2)
Type of AML - n (%)			
Primary (de novo)	213 (89.5)	216 (92.3)	429 (90.9)
Secondary	25 (10.5)	18 (7.7)	43 (9.1)
Time since original AML diagnosis (months) to randomization			
Mean (SD)	4.37 (1.273)	4.30 (1.246)	4.33 (1.259)
Median (Min, Max)	4.21 (1.5, 9.2)	4.17 (1.4, 10.9)	4.21 (1.4, 10.9)
Prior history of MDS/CMML – n (%)			
Yes	22 (9.2)	17 (7.3)	39 (8.3)[a]
Primary	20 (8.4)	17 (7.3)	37 (7.8)
Secondary	0	0	0
Missing	2 (0.8)	0	2 (0.4)

Parameter	CC-486 (N = 238)	Placebo (N = 234)	Total (N = 472)
ECOG performance status – n (%)			
Grade 0	116 (48.7)	111 (47.4)	227 (48.1)
Grade 1	101 (42.4)	106 (45.3)	207 (43.9)
Grade 2	21 (8.8)	15 (6.4)	36 (7.6)
Grade 3	0	2 (0.9)	2 (0.4)
Cytogenetic risk category at diagnosis – n (%)			
Intermediate	203 (85.3)	203 (86.8)	406 (86.0)
Poor	35 (14.7)	31 (13.2)	66 (14.0)
MRD status at randomization[b] - n (%)			
Negative	133 (55.9)	111 (47.4)	244 (51.7)
Positive	103 (43.3)	116 (49.6)	219 (46.4)
Missing	2 (0.8)	7 (3.0)	9 (1.9)
Reason ineligible for transplant[c] - n (%)			
Age	154 (64.7)	152 (65.0)	306 (64.8)
Comorbidities	52 (21.8)	50 (21.4)	102 (21.6)
Performance Status	14 (5.9)	9 (3.8)	23 (4.9)
Not acceptable or available donor	37 (15.5)	35 (15.0)	72 (15.3)
Subject decision	19 (8.0)	32 (13.7)	51 (10.8)
Unfavorable cytogenetics	6 (2.5)	10 (4.3)	16 (3.4)
Other	28 (11.8)	21 (9.0)	49 (10.4)
Received consolidation therapy following induction therapy – n (%)			
Yes	186 (78.2)	192 (82.1)	378 (80.1)
1 Cycle	110 (46.2)	102 (43.6)	212 (44.9)
2 Cycles	70 (29.4)	77 (32.9)	147 (31.1)
3 Cycles	6 (2.5)	13 (5.6)	19 (4.0)
4 Cycles	0	0	0
No	52 (21.8)	42 (17.9)	94 (19.9)
Response achieved after induction therapy (with or without consolidation therapy) – n (%)			
CR	187 (78.6)	197 (84.2)	384 (81.4)
CRi	51 (21.4)	37 (15.8)	88 (18.6)

Parameter	CC-486 (N = 238)	Placebo (N = 234)	Total (N = 472)
CR/CRi status at randomization – n (%)			
CR	183 (76.9)	177 (75.6)	360 (76.3)
CRi	50 (21.0)	44 (18.8)	94 (19.9)
Not in CR/CRi	5 (2.1)	11 (4.7)	16 (3.4)
Missing	0	2 (0.9)	2 (0.4)
Time from start of induction therapy to randomization (months)			
N	237	232	469
Mean (SD)	4.05 (1.193)	4.11 (1.420)	4.08 (1.309)
Median (Min, Max)	3.98 (1.4, 8.8)	4.01 (1.3, 15.1)	3.98 (1.3, 15.1)
Time from induction therapy to first achieving CR/CRi (days)			
N	237	232	469
Mean (SD)	46.2 (28.47)	45.0 (36.50)	45.6 (32.66)
Median (Min, Max)	36.0 (13, 242)	35.0 (14, 455)	35.0 (13, 455)
Time since first achieving CR/CRi to randomization (days)			
Mean (SD)	78.1 (30.12)	81.0 (32.19)	79.5 (31.16)
Median (Min, Max)	84.5 (7, 154)	86.0 (7, 263)	85.0 (7, 263)
Bone marrow blasts (%)			
N	238	232	470
Mean (SD)	2.13 (1.481)	2.19 (1.512)	2.16 (1.495)
Median (Min, Max)	2.00 (0.0, 5.0)	2.00 (0.0, 6.5)	2.00 (0.0, 6.5)
Peripheral blood blasts (%)			
N	230	232	452
Mean (SD)	0.1 (0.26)	0.0 (0.29)	0.1 (0.28)
Median (Min, Max)	0.0 (0, 2)	0.0 (0, 2)	0.0 (0, 2)

AML = acute myeloid leukemia; CMML = chronic myelomonocytic leukemia; CR = complete remission; CRi = complete remission with incomplete blood count recovery; ECOG = Eastern Cooperative Oncology Group; Max = maximum; MDS = myelodysplastic syndromes; Min = minimum; MRD = minimal residual disease; SD = standard deviation.

a. Number of subjects with history of prior MDS/CMML differs from the number of subjects with secondary AML by 4 subjects because 2 subjects (2511001 and 8601006, both randomized to CC-486) had AML secondary to previous chemotherapy (ie, therapy-related AML), 1 subject (7011007 randomized to the CC-486 group) had AML secondary to CMML but it was not reported as prior history of CMML, and 1 subject (8601021 randomized to placebo) had secondary AML but no documented history of MDS/CMML.

b. During the Screening period

c. A subject may have had more than 1 reason.

Notes: Time interval in days was calculated as the difference between the randomization date and the date of interest (eg, date of original AML diagnosis) plus 1 day. Time interval presented in month is transformed from days to months by using conversion formula: months = days/30.4375.

Numbers analysed

All primary and secondary clinical efficacy evaluations were conducted using the ITT population, which included all 472 randomized subjects. The mITT population, which was used for supportive analysis of the primary and key secondary efficacy endpoints, included 440 (93.2%) subjects who received a minimum of 1 cycle of treatment, had CR/CRi at baseline, as programmatically determined by central laboratory data, and satisfied all eligibility criteria.

Table 15: Analysis Sets in Study CC-486-AML-001

Analysis Set	CC-486 (N = 238)	Placebo (N = 234)	Total (N = 472)
Intent-to-treat	238	234	472
Modified intent-to-treat	223	217	440
Safety	236	233	469
HRQoL evaluable (FACIT-Fatigue Scale)	225	219	444
HRQoL evaluable (EQ-5D-3L)	225	217	442

EQ-5D-3L = European quality of life–five dimensions-three levels; FACIT = Functional Assessment of Chronic Illness Therapy; HRQoL = health-related quality of life.
Source: CSR CC-486-AML-001 Table 6, HRQoL Table 14.3.6.3.1.1, and HRQoL Table 14.3.6.3.2.1.

The difference of 32 patients between ITT and mITT groups is not expected to have a major influence on the outcome of the study.

Outcomes and estimation

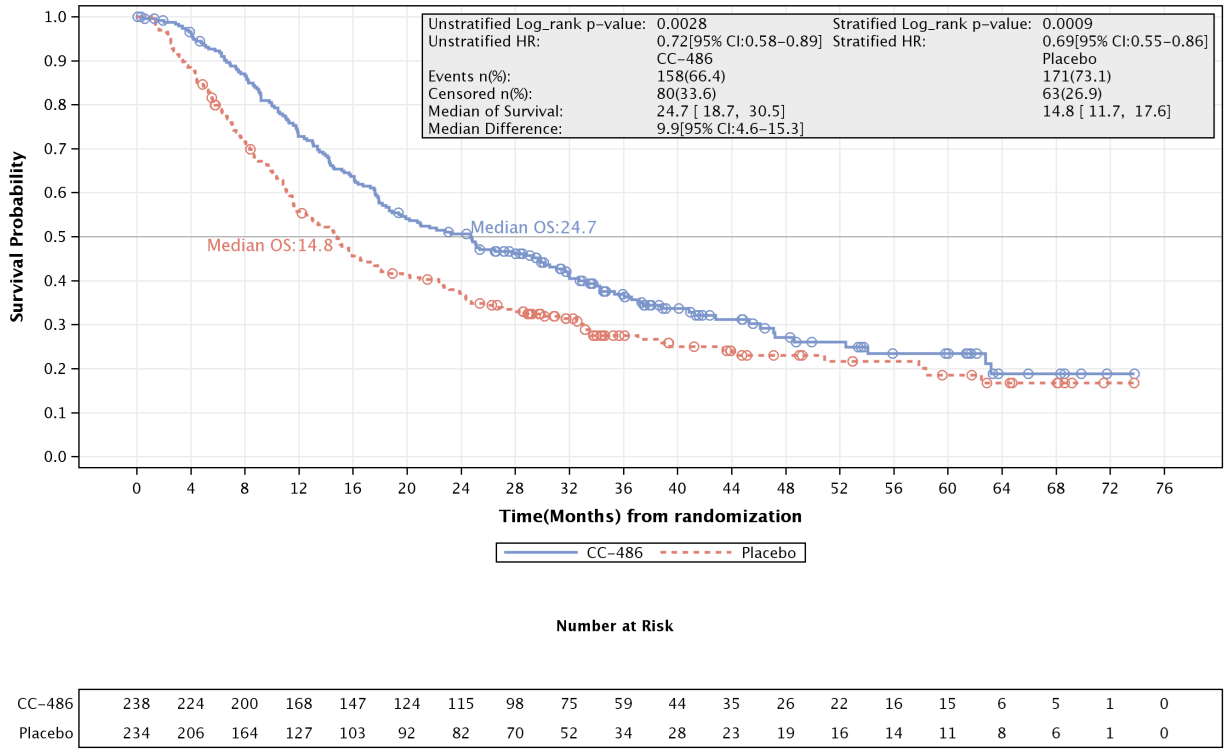
Primary Efficacy Endpoint: Overall Survival

The primary endpoint of the CC-486-AML-001 study was OS defined as time from randomization to death from any cause.

Table 16: Efficacy Results of Overall Survival from Study CC-486-AML-001 (ITT Population)

Efficacy Endpoint Statistic	CC-486 N = 238	Placebo N = 234
Overall Survival		
Number of deaths, n (%)	158 (66.4)	171 (73.1)
Subjects censored, n (%)	80 (33.6)	63 (26.9)
Median overall survival (months) (95% CI)[a]	24.7 (18.7, 30.5)	14.8 (11.7, 17.6)
Hazard ratio$_{C/P}$ (95% CI)[b]	0.69 (0.55, 0.86)	
Stratified log-rank test: p-value [c]	0.0009	

Figure 2. Kaplan-Meier Plot of Overall Survival for CC-486 Versus Placebo (ITT Population)



CC-486	238	224	200	168	147	124	115	98	75	59	44	35	26	22	16	15	6	5	1	0
Placebo	234	206	164	127	103	92	82	70	52	34	28	23	19	16	14	11	8	6	1	0

The analysis for OS was repeated using de modified ITT population (included all subjects who met eligibility criteria, experienced no protocol violations during the study, and received a minimum of 1 cycle of treatment). The results were consistent with those of the primary analysis with a significantly improved OS for CC-486 versus placebo (stratified log-rank test nominal p-value = 0.0004). The median OS in the mITT population was 24.8 months for the CC-486 group and 14.6 months for the placebo group, with a clinically meaningful difference in median OS of 10.2 months with CC-486 treatment. The HR was 0.66 (95% CI: 0.53, 0.83), indicating a 34% reduction in the risk of death for the CC 486 group.

Additional pre-specified sensitivity analyses were performed to assess the impact of censoring on the primary analysis due to subjects who withdrew consent from survival follow-up, and the potentially confounding effects of other cancer therapies received subsequent to the study therapy on OS. These additional sensitivity analyses were based on the ITT population and analyzed using the same methods described previously for the primary efficacy endpoint.

The analyses for subsequent therapies included:

- Censoring for the use of any subsequent therapy (including post-treatment transplant) for AML. For this analysis, subjects who received any subsequent therapy for AML following discontinuation from study treatment were censored on the earlier date of the first subsequent therapy, or transplant date, regardless of survival status at the time of the final analysis.
- Censoring for the use of disease-modifying subsequent AML therapy, defined as any subsequent AML therapy that is not hydroxycarbamide.

- Censoring for post-treatment transplant at the time of the transplant.

In all cases, the results were generally consistent with the primary analysis with hazard ratios favoring CC-486 over placebo (data not shown), demonstrating the robustness of the treatment effect.

Secondary Endpoint: Relapse-Free Survival

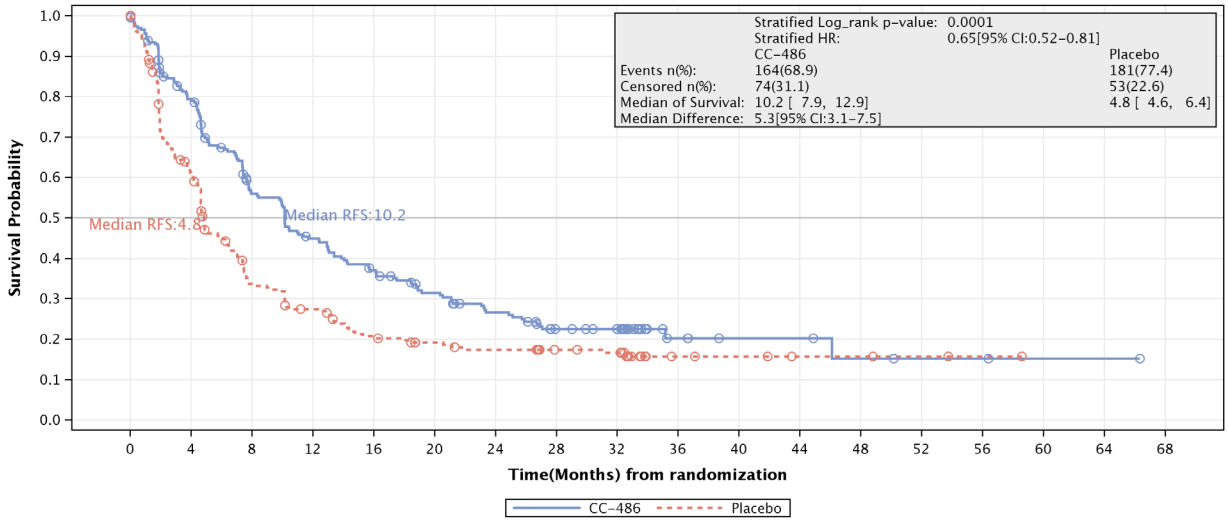
The key secondary objectives included the effect of CC-486 on RFS, assessed as the time from the date of randomization to the date of documented relapse or death from any cause, whichever occurred first.

Table 17:Efficacy Results of Relapse-free Survival from Study CC-486-AML-001 (ITT Population)

Efficacy Endpoint **Statistic**	**CC-486** **N = 238**	**Placebo** **N = 234**
Relapse-free Survival		
Number of relapsed or died, n (%)	164 (68.9)	181 (77.4)
Subjects censored, n (%)	74 (31.1)	53 (22.6)
Median relapse-free survival (months) (95% CI)[a]	10.2 (7.9, 12.9)	4.8 (4.6, 6.4)
Hazard ratio$_{C/P}$ (95% CI)[b]	0.65 (0.52, 0.81)	
Stratified log-rank test: p-value [c]	0.0001	

CI = confidence interval; C/P = CC-486/placebo; ITT = intent-to-treat.
a Median estimate of OS and RFS is from an unstratified Kaplan-Meier analysis.
b The hazard ratio is from a Cox proportional hazards model stratified by age, cytogenetic risk category, and received consolidation therapy or not.
c The p-value is 2-sided from a log-rank test stratified by age, cytogenetic risk category, and received consolidation therapy or not.

Figure 3. Kaplan-Meier Plot of Relapse-free Survival: CC-486 Versus Placebo (Intent-to-Treat Population)



Number at Risk

CC-486	238	173	116	92	75	60	47	32	29	8	5	5	3	2	2	1	1	0
Placebo	234	136	70	55	40	33	29	24	22	6	5	3	3	2	1	0		

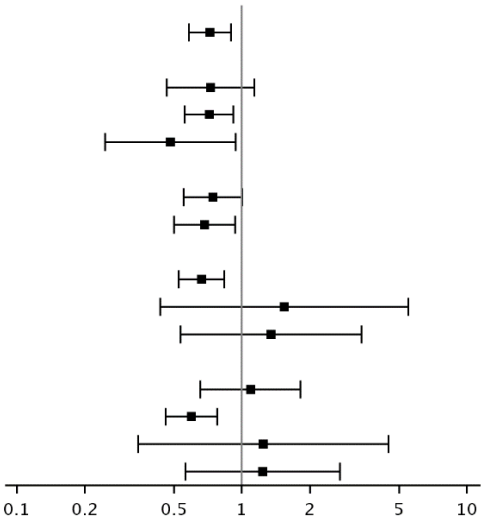
Ancillary analyses

The Overall Survival was analyzed by prespecified subgroups considering demographic characteristics and prognostic factors, with potential to influence the outcome of disease.

Demographic Subgroups

The OS was improved for several demographic subgroups, namely age, sex, race, and geographic region.

Figure 4. Forest Plot of Overall Survival by Demographic Subgroup (ITT Population)



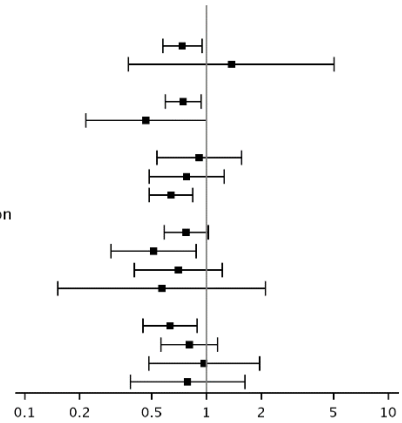
Subgroup	CC-486 n/N[a]	Placebo n/N[a]	HR(95%CI)	CC-486 [b]	Placebo [b]
Overall	158/238	171/234	0.72(0.58, 0.89)	24.7	14.8
Age group					
>=55 to <65	36/66	41/68	0.72(0.46, 1.13)	31.6	15.2
>=65	122/172	130/166	0.71(0.56, 0.92)	19.9	14.3
>=75	19/28	18/24	0.48(0.25, 0.94)	24.8	9.9
Sex					
Male	79/118	93/127	0.74(0.55, 1.00)	21.7	15.9
Female	79/120	78/107	0.68(0.50, 0.93)	25.0	11.6
Race					
White	144/216	148/197	0.66(0.53, 0.83)	25.0	13.4
Asian	3/6	14/20	1.54(0.43, 5.47)	9.1	14.6
Black or Other	9/14	9/17	1.35(0.53, 3.40)	18.3	27.7
Geographic Region					
North America	29/37	30/42	1.09(0.65, 1.82)	15.3	15.2
Europe	111/167	114/147	0.60(0.46, 0.77)	28.6	13.0
Asia	3/6	13/17	1.24(0.35, 4.48)	9.1	14.6
Australia	14/26	11/23	1.23(0.56, 2.72)	20.2	37.1

CI = confidence interval; ITT = intent-to-treat; OS = overall survival.
a Number of events/number of subjects.
b Median OS in months.

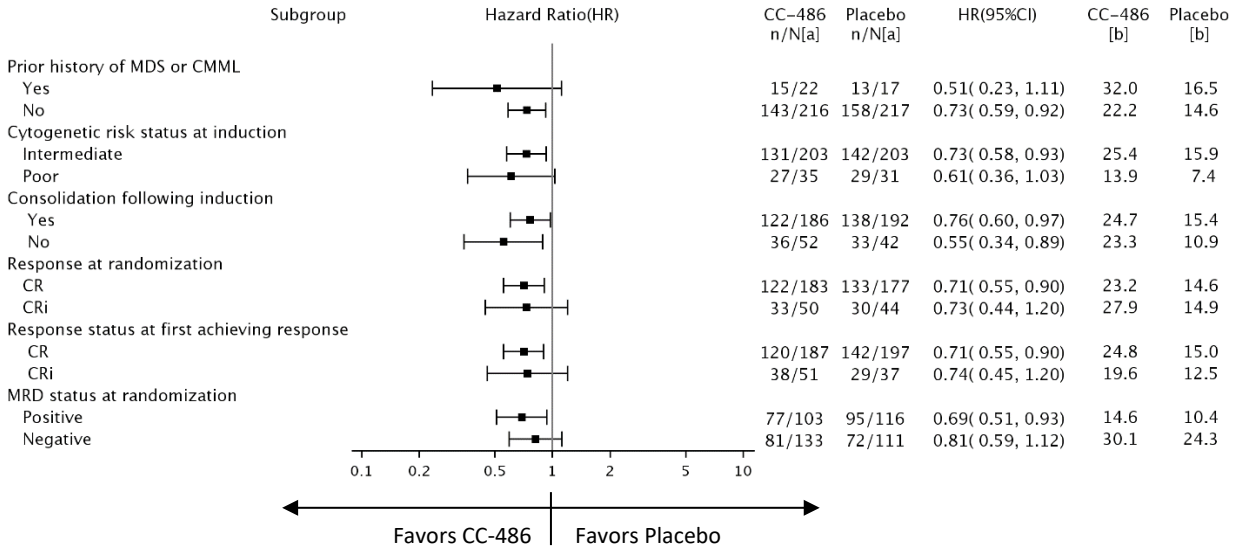
Disease-related Subgroups

The Overall Survival was analyzed according different disease-related subgroups.

Figure 5. **Forest Plot of Overall Survival by Baseline Disease Characteristics (ITT Population)**



Subgroup	CC-486 n/N[a]	Placebo n/N[a]	HR(95%CI)	CC-486 [b]	Placebo [b]
Consolidation cycles					
1 or 2 cycles	118/180	132/179	0.74(0.57, 0.94)	24.7	14.9
3 or 4 cycles	4/6	6/13	1.37(0.37, 5.02)	25.5	NA
ECOG performance status					
0 or 1	144/217	157/217	0.74(0.59, 0.93)	24.7	14.9
2 or 3	14/21	14/17	0.46(0.22, 1.00)	22.2	11.2
WHO AML classification					
AML with Recurrent Genetic Abnormalities	25/39	29/46	0.91(0.53, 1.56)	21.9	17.6
AML with Myelodysplasia-Related changes	35/49	34/42	0.78(0.48, 1.25)	19.9	14.8
AML-Not Otherwise Specified	96/148	108/145	0.64(0.48, 0.84)	25.1	13.4
CR/CRi at randomization and use of consolidation					
CR with Consolidation	97/145	104/141	0.77(0.59, 1.02)	23.2	15.2
CR without Consolidation	25/38	29/36	0.51(0.30, 0.88)	23.3	11.2
CRi with Consolidation	23/37	27/40	0.70(0.40, 1.22)	29.6	17.6
CRi without Consolidation	10/13	3/4	0.57(0.15, 2.10)	27.9	4.6
CR/CRi and MRD at randomization					
CR with MRD+	61/85	72/87	0.63(0.45, 0.89)	15.3	10.8
CR with MRD-	61/97	58/85	0.80(0.56, 1.15)	29.7	23.9
CRi with MRD+	14/16	18/23	0.97(0.48, 1.95)	11.5	10.8
CRi with MRD-	19/33	12/20	0.79(0.38, 1.63)	29.3	29.9



AML = acute myeloid leukaemia; CI = confidence interval; CMML = chronic myelomonocytic leukaemia; CR = complete remission; CRi = complete remission with incomplete blood count recovery;
ECOG = Eastern Cooperative Oncology Group; ITT = intent-to-treat; MDS = myelodysplastic syndromes; MRD = minimal residual disease; OS = overall survival; WHO = World Health Organization.
a Number of events/number of subjects.
b Median OS in months.
Note: AML classification based on WHO, 2008.

Summary of main study

The following Table 25 summarise the efficacy results from the main studies supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 18: Summary of Efficacy for trial CC-486-AML-001

Title: A Phase 3, randomized, double-blind, placebo-controlled study to compare efficacy and safety of oral azacitidine (CC-486) plus BSC versus BSC as maintenance therapy in subjects with AML in complete remission	
Study identifier	PROTOCOL NUMBER: CC-486-AML-001 EudraCT NUMBER: 2012-003457-28

Design	Study CC-486-AML-001 was an international, multicenter, placebo-controlled, Phase 3 study with a double-blind, randomized, parallel-group design in subjects with de novo AML or AML secondary to prior diagnosis of MDS or CMML. The study planned to enroll approximately 460 subjects aged ≥ 55 years, who were in first CR/CRi following intensive induction therapy with or without consolidation chemotherapy. Subjects with CR/CRi after HMA treatment, subjects with good risk cytogenetics and those who were candidates for HSCT, were excluded. Randomization was stratified by the following key prognostic factors: • age (55 to 64 years/ ≥ 65 years), • prior history of MDS (yes/no), • cytogenetic risk category at the time of induction therapy (intermediate risk/poor risk), and • receipt of consolidation therapy (yes/no)		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 months 28 days Until progression
Hypothesis	Superiority		
Treatments groups: subjects, aged 55 or older, diagnosed with AML or AML secondary to prior myelodysplastic disease or CMML, and who have achieved CR/CRi following induction with or without consolidation chemotherapy.	CC-486 arm Patients with AML in CR/CRi		238 patients were randomized and treated with CC-486 The median treatment duration was 11.6 months (range: 0.5 to 74.3 months) for the CC-486 group. The median number of cycles received in the CC-486 group was 12.0 (range: 1.0 to 80.0).
	Placebo arm Patients with AML in CR/CRi		234 patients were randomized and treated with placebo. The median treatment duration was 5.7 months (range: 0.7 to 68.5 months) for the placebo group. The median number of cycles received in the placebo group was 6.0 (range: 1.0 to 73.0).
Endpoints and definitions	Primary endpoint Overall Survival	OS	Defined as the time from randomization until death from any cause.
	Secondary endpoint Relapse Free Survival	RFS	Defined as the time from randomization to the date of first documented relapse or death from any cause, whichever occurred first.
Database lock	15 Jul 2019		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	Efficacy analyses were performed using the ITT population, defined as all subjects who were randomized, independent of whether they received study treatment or not.			
Descriptive statistics and estimate variability	Treatment group	CC-486 arm	Placebo arm	Total
	Number of subjects	n=238	n=234	n=472
	OS Median (months)	24.7 months	14.8 months	
	(95% CI)	(18.7, 30.5)	(11.7, 17.6)	
	HR	0.69 (0.55, 0.86)		
	Stratified log-rank test:	p=0,0009		
	RFS Median (months)	10.2 months	4.8 months	
	(95% CI)	(7.9, 12.9)	(4.6, 6.4)	
	HR	0.65 (0.52, 0.81)		
	Stratified log-rank test:	p=0.0001		
Effect estimate per comparison	OS According disease-related subgroups	Comparison groups		
		CR status	HR = 0.71 (95% CI: 0.55, 0.90)	
		CRi status	HR = 0.73 (95% CI: 0.44, 1.20)	
		MRD-positive	HR = 0.69 (95% CI: 0.51, 0.93)	
		MRD-negative	HR = 0.81 (95% CI: 0.59, 1.12)	
		Intermediate Cytogenetic risk	HR = 0.73 (95% CI: 0.58, 0.93)	
		Poor Cytogenetic risk	HR = 0.61 (95% CI: 0.36, 1.03)	
		Comparison groups		
		CR status	HR = 0.66 (95% CI: 0.52, 0.84)	

	RFS According disease-related subgroups	CRi status	HR = 0.59 (95% CI: 0.36, 0.97)
		MRD-positive	HR = 0.58 (95% CI: 0.43, 0.78)
		MRD-negative	HR = 0.71 (95% CI: 0.52, 0.98)
		Intermediate Cytogenetic risk	HR = 0.66 (95% CI: 0.52, 0.83)
		Poor Cytogenetic risk	HR = 0.61 (95% CI: 0.35, 1.04)

Analysis performed across trials (pooled analyses and meta-analysis)

Clinical studies in special populations

Table 19:**Number of Elderly Patients Included in the Population PK Analysis**

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials CC-486-AML-001	286/472 (60.6%)	52/472 (11.0%)	1/472 (0.2%)

Supportive studies

Support for the activity of azacitidine in active AML is provided by Phase 3 Study AZA-AML- 001, which used the SC formulation of azacitidine, and three Phase 1 studies with oral formulations of azacitidine ((AZA-MDS-004, AZA PH US 2008 CL 008, and AZA PH US 2007 CL 005).

Study AZA-AML- 001

Study AZA-AML-001 is a completed international, multicenter, controlled, Phase 3 study with an open-label, randomized, parallel-group design.

The study was set up with 3 phases: a Pre-randomization Phase, a Treatment Phase, and a Follow-up Phase. Following screening for eligibility, enrolled subjects were assigned by the Investigator to 1 of 3 CCRs, based on local practice and an evaluation of the subject's underlying disease condition, as follows:

- Intensive chemotherapy using IV cytarabine in conjunction with an anthracycline in a 7 + 3 regimen, plus BSC;
- Low-dose cytarabine 20 mg SC BID for 10 days, every 28 days, plus BSC;
- Best supportive care only.

The study enrolled and treated 488 subjects. The experimental arm consisted of 241 subjects, the control arm of 247 subjects. The experimental arm received Azacitidine 75 mg/m^2/day SC the control arm, CCR assigned by the investigator prior to randomization. Azacitidine was administered in a dose of 75 mg/m^2/day SC for 7 days of every 28 day cycle.

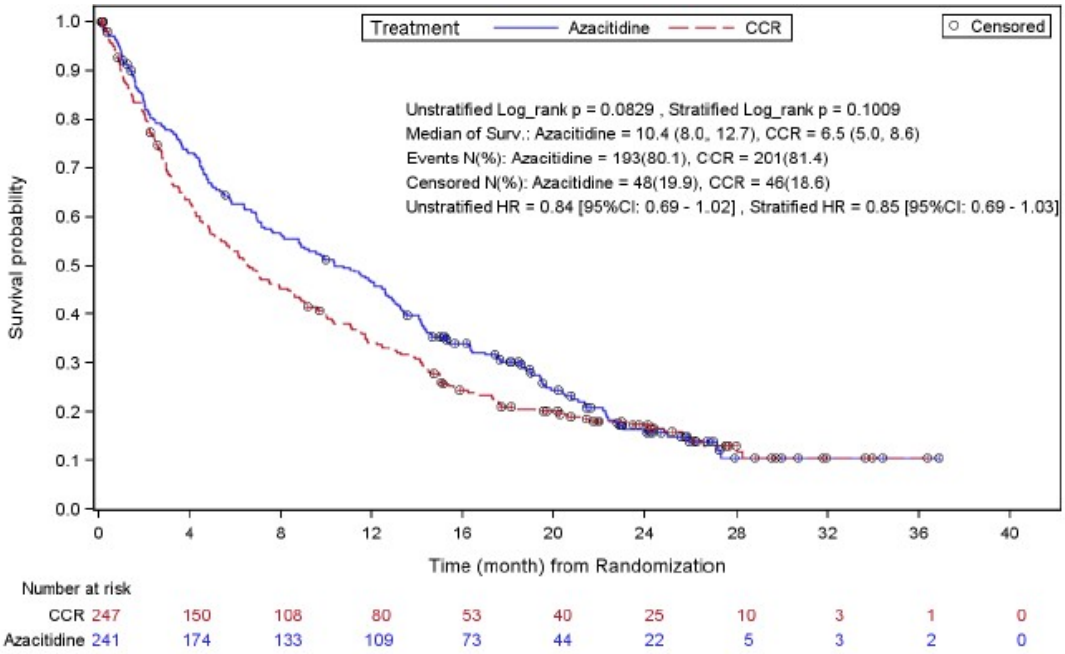
Overall survival was the primary endpoint of the study and was evaluated from the time of randomization to death from any cause. RFS was the key secondary endpoint. Additional secondary efficacy endpoints included time to relapse and time to discontinuation from treatment, which supplement the primary and key secondary efficacy endpoints by providing additional temporal perspectives.

Study results:

Primary efficacy endpoint – overall survival

The median OS was 10.4 months in the azacitidine group compared with 6.5 months in the combined CCR group, a clinically meaningful increase in median survival of 3.8 months with a corresponding 15% reduced risk of death (HR = 0.85; 95% CI = 0.69, 1.03; stratified log rank p = 0.1009)

Figure 6: Kaplan-Meier Plot of Time to Death from Any Cause (Intent-to-treat Population)



Secondary efficacy endpoints:

The results for secondary endpoints were consistent with the improvement seen in the primary endpoint of OS.

A clinically meaningful difference of 12.3% in one-year survival estimate was observed in favor of azacitidine (46.5% in the azacitidine group versus 34.3% in the CCR group). Consistent results were observed for one-year survival in post hoc analyses. A clinically meaningful increase in the one-year survival estimate of 12.2% and 14.9% were observed in the post hoc mITT and regression based imputation analyses in favor of azacitidine, respectively.

A trend toward improved median EFS was observed with azacitidine compared with the CCR treatment group (6.7 months in the azacitidine group versus 4.8 months in the CCR group) and similar median RFS were observed (9.3 months in the azacitidine group versus 10.5 months in the CCR group).

Similar overall response rate (CR + CRi) as determined by the IRC were observed between azacitidine and CCR treatment groups (27.8% in the azacitidine group [19.5% CR] compared to 25.1% in the CCR group [21.9% CR]). The median duration of remission was 10.4 months for the azacitidine subjects versus 12.3 months for the CCR subjects.

Study AZA-MDS- 003

This was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study design, with the aim of comparing the efficacy and safety of oral azacitidine to placebo in subjects with RBC transfusion-dependent anemia and thrombocytopenia (platelet count ≤ 75 × 109/L) due to lower-risk MDS.

The study enrolled 216 subjects at 101 sites globally.

The enrolled study subjects represent a subset of the IPSS lower-risk MDS population with both RBC transfusion-dependent anemia and thrombocytopenia, and therefore has a far poorer prognosis than would be expected for the general group of patients with lower risk disease. The study consisted of 4 phases: Screening, Double-blind treatment, Follow-up, and Extension.

This study is still on-going; the Applicant submitted an interim report.

Study results:

Primary efficacy endpoint – RBC-TI

The primary efficacy endpoint is RBC-TI with duration ≥ 56 days (8 weeks). As of the cut-off date, a greater proportion of subjects in the oral azacitidine treatment group achieved the primary efficacy endpoint (30.8% of subjects) than in the placebo treatment group (11.9% of subjects).

The difference in the proportion of subjects with RBC-TI with duration ≥ 56 days between the 2 treatment groups was 18.9%. Statistically significant ($p < 0.0005$) results favoured the CC-486 treatment group over placebo treatment group.

The analysis for the primary endpoint in the mITT population was consistent with that of the ITT population.

Secondary efficacy endpoints

Time to RBC transfusion independence

Table 20: Summary of Time to Red Blood Cell Transfusion Independence for at Least 56 Days Among Subjects Who Achieved RBC-TI for at Least 56 Days on Treatment (ITT Population)

Parameter	CC-486 (N = 33)	Placebo (N = 13)
Time to response (months)		
Mean	3.30	2.89
SDev	2.683	3.744

Median	2.37	2.04
Q1, Q3	1.71, 4.27	0.99, 2.40
Min, max	0.0, 10.9	0.0, 14.3
Time to response[a] (months) category – n (%)		
Day 1 to ≤ 1 month	4 (12.1)	5 (38.5)
> 1 months to ≤ 2 months	9 (27.3)	1 (7.7)
> 2 months to ≤ 3 months	7 (21.2)	4 (30.8)
> 3 months to ≤ 4 months	2 (6.1)	0
> 4 months to ≤ 5 months	6 (18.2)	1 (7.7)
> 5 months to ≤ 6 months	1 (3.0)	1 (7.7)
> 6 months to ≤ 8 months	0	0
> 8 months to ≤ 10 months	3 (9.1)	0
> 10 months to ≤ 12 months	1 (3.0)	0
> 12 months	0	1 (7.7)

ITT = intent-to-treat; max = maximum; min = minimum; Q1 = first quartile; Q3 = third quartile; RBC = red blood cells; SDev = standard deviation; TI = transfusion independence.

[a] Percentages are based on the number of responders of RBC-TI for at least 56 days in each category group.

Note: Time to RBC-TI for at least 56 days is defined as the time between randomization and the date onset of TI is first observed. Only subjects who achieved RBC-TI for at least 56 days are summarized.

2.5.3. Discussion on clinical efficacy

AML is a rare, heterogeneous, and aggressive hematologic malignancy characterized by rapid progression of the disease and symptoms and is uniformly fatal if not treated.

Azacitidine is an analogue of the naturally occurring pyrimidine nucleoside cytidine and is classified as an antimetabolite. Vidaza, the injectable formulation of the same active ingredient azacitidine, is considered a standard of care for patients with AML who are ineligible to receive intensive chemotherapy globally.

The oral form of azacitidine was developed to allow sustained and extended administration of azacitidine at lower systemic doses than can be practically achieved with parenteral therapy.

The proposed starting dose is 300 mg orally, once daily (QD) for the first 14 days of each 28-day cycle. In the case of disease relapse during therapy with 5% to 15% blasts in peripheral blood or bone marrow, in conjunction with clinical assessment, the dosing schedule may be extended from 14 days to 21 days of repeated 28-day cycles.

A dedicated dose response study with the to-be-marketed oral formulation of azacitidine tablets has not been submitted. According to the Applicant, the cumulative data support the 300 mg QD dose for 14 out of 28 days as the appropriate oral azacitidine dose for maintenance therapy for patients with AML who have achieved CR or CRi after intensive induction therapy with or without consolidation. The approach of the Applicant can be considered acceptable.

Design and conduct of clinical studies

This application is mainly supported by the following study:

- a pivotal phase 3 study CC-486-AML-001 and

Phase 1 studies (AZA-MDS-004, AZA PH US 2008 CL 008, and AZA PH US 2007 CL 005) can only be considered as supportive and exploratory of the proposed dose regimen.

Study CC-486-AML-001 was a Phase 3, double-blind, randomized, placebo-controlled, multicenter study designed to compare the efficacy and safety of CC-486 plus BSC to placebo plus BSC as maintenance therapy in subjects who achieved CR/CRi after induction with intensive chemotherapy with or without consolidation.

Population

The study enrolled subjects who were in first CR/CRi following intensive induction chemotherapy with or without consolidation chemotherapy. Subjects with CR/CRi after treatment with hypomethylating agents (HMAs), subjects with good risk cytogenetics, and those who were candidates for HSCT were excluded.

One of two amendments introduced to the protocol CC-486-AML-001 concerned the modification of the Inclusion Criterion #4 to change the amount of time required for subjects to be in complete remission (CR) or in complete remission with incomplete blood count recovery (CRi) from 3 months to 4 months (± 7 days). This amendment had the potential to increase the number of patients included in the trial with best prognostic factors, that were able to maintain the response for a long period of time. However, in the applicant's opinion this effect would not influence the final results of the study, because the randomization would be a guarantee that the proportion of patients with better prognosis would be balanced between both arms. In fact, according to the applicant's response, the number of subjects that received 1 or 2 cycles of consolidation was equal distributed between the treatment arms and the median time from first achieving CR to randomization was 85

days for all patients, and 84.5 days for the oral azacitidine group and 86 days for the placebo group. The explanation provided in the applicant's response is considered acceptable.

Study CC-486-AML-001 randomized 472 subjects (238 to CC-486 and 234 to placebo) at 147 investigational sites. The subject population comprised adult subjects (median age of 68.0 years, range 55 to 86 years) of both genders (51.9% male) who were predominantly white (87.5%). Subjects had been diagnosed with de novo (90.9%) or secondary (9.1%) AML with intermediate (86.0%) or poor (14.0%) cytogenetic risk at diagnosis. Subjects were in CR (81.4%) or CRi (18.6%) after induction therapy with or without consolidation therapy. The median time from first achieving CR/CRi to randomization was 85.0 days. The majority of subjects (80.1%) had received consolidation therapy. At randomization, 51.7% of subjects were minimal residual disease (MRD) negative and 46.4% were MRD positive.

The study population can be considered appropriate and selected avoid enrichment. Study participants can be considered representative for the therapeutic indication of azacitidine.

Duration

The median treatment duration was 11.6 months for the oral azacitidine group and 5.7 months for the placebo group; the median number of cycles received was 12.0 and 6.0, respectively. Such duration is considered acceptable for an already approved substance.

Endpoints

The primary endpoint was OS, defined as the time from randomization until death from any cause. The key secondary endpoint was RFS, defined as the time from randomization to the date of first documented relapse or death from any cause, whichever occurred first. Crossover between the treatment groups was not allowed so as to minimize the confounding impacts on the assessment of OS. The primary efficacy variable, defined as time from randomization to death from any cause, and the primary efficacy analysis for OS were performed using the ITT population.

The endpoints are considered appropriate for the proposed therapeutic indications of the oral form of an already approved active substance.

Efficacy data and additional analyses

Study CC-486-AML-001 results demonstrated significantly longer OS and RFS with oral azacitidine versus placebo (stratified log-rank test p = 0.0009 for OS and p = 0.0001 for RFS). The median OS was 24.7 months for the oral azacitidine group and 14.8 months for the placebo group after a median follow-up time of 41.2 months based on reverse Kaplan-Meier method, with a clinically meaningful difference in median OS of 9.9 months with CC-486 treatment. The hazard ratio (HR) was 0.69 (95% confidence interval [CI]: 0.55, 0.86), indicating a 31% reduction in the risk of death for the oral azacitidine group. The median RFS was 10.2 months for the oral azacitidine group and 4.8 months for the placebo group, with a clinically meaningful difference in median RFS of 5.4 months with oral azacitidine treatment. The HR was 0.65 (95% CI: 0.52, 0.81), indicating a 35% reduction in risk of relapse or death for the oral azacitidine group. A lower death rate was observed in the oral azacitidine group compared with the placebo group as early as 90 days after randomization (4 [1.7%] subjects versus 20 [8.5%] subjects, respectively).

The improvement in OS was seen in different subgroups of patients and was particularly strong among patients older than 65 years (HR = 0,71 (0,56 a 0,92)) and patients older than 75 years (HR = 0,48 (0,25 a 0,94)),

which is clinically relevant, because at these ages the patients are not eligible to bone marrow transplant and the risk of relapse is very high.

The proportion of subjects surviving at the 1-year time point was 72.8% in the oral azacitidine group and 55.8% in the placebo group, for a difference of 17.0%. The proportion of subjects surviving at the 2-year time point was 50.6% in the oral azacitidine group and 37.1% in the placebo group, for a difference of 13.5%.

The probability of RFS at the 6-month time point was 67.4% in the oral azacitidine group and 45.2% in the placebo group, for a difference of 22.2%. The probabilities of RFS were consistently higher for the oral azacitidine group than for the placebo group at each of the later time points (44.9% versus 27.4%, respectively, at 1 year and 26.6% versus 17.4% at 2 years), demonstrating durable efficacy over time for oral azacitidine treatment. Sensitivity analyses of OS and RFS provided support for the robustness and consistency of the results of the primary and key secondary efficacy endpoints.

A 9.9-month improvement in median OS in the oral azacitidine treatment was reached, compared with the placebo, however after 48 months the survival probability was very close to each other in both arms and the Kaplan-Meier curves were almost overlapping from 64 months onwards. The provided updated OS data from 15 Oct 2019 and 20 Sep 2020 (providing 3 and ~14 additional months of follow-up, respectively) and RFS data from 15 Oct 2019 (3 additional months of follow-up) are consistent with the results from the earlier data cut (15 Jul 2019) reported in the clinical study report (CSR), with unchanged median OS and RFS and HR with additional follow-up, demonstrating the robustness of the results. Furthermore, the tail end of the updated OS and RFS curves showed increased separation compared with those from the earlier data cut provided in the CSR. It is agreed that the updated data support the original conclusion that oral azacitidine maintenance therapy has significant impact on survival and delay of relapse in subjects who achieved CR/CRi following intensive chemotherapy.

Other secondary endpoints (time to relapse and time to discontinuation from treatment) also demonstrated the benefit of oral azacitidine as maintenance therapy for the treatment of AML. The median time to relapse was 10.2 months in the oral azacitidine group and 4.9 months in the placebo group. The median time to treatment discontinuation for any reason was 11.4 months in the oral azacitidine group and 6.1 months in the placebo group.

Study CC-486-AML-001 also demonstrated that subjects receiving oral azacitidine, compared with those receiving placebo, had significantly lower rates of hospitalization events (0.48 events per person-year for the oral azacitidine group and 0.64 events per person-year for the placebo group; nominal $p = 0.0068$) and number of days hospitalized (7.89 days per person-year for oral azacitidine compared with 13.36 day per person-year for placebo; nominal $p < 0.0001$).

The results for the secondary endpoints corroborated the results seen with the primary endpoint.

The results demonstrated that oral azacitidine, as maintenance therapy, significantly improved OS and RFS, while maintaining HRQoL comparable to placebo and the general population. Results from the hospitalization analyses indicate that treatment with oral azacitidine can potentially lead to a reduction in healthcare resource utilization associated with hospitalizations.

It has been noted that a large percentage of patients in both groups discontinued treatment (81.9% and 88.9% for oral azacitidine and placebo respectively) mainly due to disease relapse. This is not considered uncommon.

In the subgroup analysis, it appears that only in European population the effect of oral azacitidine was favourable. The Applicant performed additional analyses that showed that regional or racial differences in the OS and RFS benefit associated with oral azacitidine treatment were likely due to larger variability caused by

small sample size. The overall study results can be applied to the global population and not only to the European population and a similar clinical benefit from oral azacitidine treatment is expected in the overall study population. This is due to the following:

1) There are no notable differences in treatment practices across North America and EU, and OS and RFS are similar for patients treated with oral azacitidine in both regions.

2) The statistical assessment including post-hoc subgroup analyses, multivariate analyses all support that the overall results from the ITT analysis are applicable to both regions.

The effect on the probabilities of RFS from the 36 months onward observation in the pivotal study.

The applicant adequately discussed the reason of not including exploratory endpoints in the study protocol, i.e. measures of cytogenetics, DNA methylation, single nucleotide polymorphism, gene sequencing, gene expression, micro-ribonucleic acid expression and/or cellular protein expression. Certain endpoints i.e. high resolution DNA methylation and next generation sequencing (NGS) were not available at the time of protocol development. The Applicant has completed several exploratory analyses, which are provided in separate reports: CC-486 (QUAZAR) AML-001: Analyses of exploratory minimal residual disease (MRD) data and correlative studies with clinical endpoints and CC-486-AML-001: Analyses of Pharmacodynamic Changes of CC-486 and Correlative Studies with CC-486 Drug Exposure and Clinical Endpoints.

In some subgroups of disease-related factors, mainly patients in CRi or patients with MRD-negative after randomization, the evidence of observed benefit was not so strong with a HR = 0.74 (0,45 to 1.20) for CRi subgroup and HR = 0.81 (0,59 to 1.12) for the MRD-negative subgroup.

Although it has been shown that in the population of subjects aged ≥ 65 years suffering from newly diagnosed AML with a BM blast count > 30% and not eligible for HSCT, treatment with azacitidine resulted in a median OS of 10.4 months, a clinically meaningful increase of 3.8 months over CCR with an increase of 12.3% in the 1-year survival estimate over CCR, the primary OS analysis did not meet the conventional level of statistical significance.

It would have been expected that the final results Study AZA-MDS-003 could provide confirmatory support of the efficacy and safety of oral azacitidine. However, the primary objective of the trial was not related to OS or RFS. The objective was to evaluate RBC Transfusion Independence (RBC-TI) in each of the 2 treatment groups (oral azacitidine [CC-486] versus placebo) in subjects with RBC transfusion-dependent anemia and thrombocytopenia due to IPSS lower-risk MDS. However, subjects were treated for vitamin B12 deficiency. This makes the interpretation of the interim results difficult. The Applicant clarified that all 3 subjects in Study AZA-MDS-003 were treated with vitamin B12 only following the diagnosis of deficiency. No other subjects received vitamin B12 during the study to correct potential B12 deficiency.

In respect to the design of the pivotal study, the applicant was asked to clarify the rational for the possibility of the extension of treatment after relapse from 14 to 21 days of oral azacitidine in the experimental arm, as it would not be expected that a patient progressing on maintenance treatment would be able to respond with an increase of dose as no data was presented to suggest any effectiveness of this option. In addition, safety data analyses suggest that this schedule should be avoided as patients present a higher rate of serious TEAE and TEAE leading to death. According with the applicant there was evidence from the study AZA PH US 2007 CL 005 that the extension of the treatment to 21 days was well tolerated and only minimal associated with an increase in AEs. The applicant also considered that because of the interpatient variability in oral azacitidine drug absorption, extending the dosing schedule to 21 days would provide more drug exposure of leukemic cells and increase the probability of response. However, according to the results of overall response rate provided by the

applicant, 23,3% of the subjects in the oral azacitidine group and in 11,4% in the control group achieved CR/CRi. Considering the number of patients included in the extension program and the difference in overall response that was obtained, it is difficult to demonstrate that extending the treatment period after relapse increases the overall response rate in comparison with placebo. However, in the absence of new safety signals, in cases of disease relapse, with 5% to 15% blasts in peripheral blood or bone marrow, in conjunction with a clinical assessment, an extension of the dosing schedule from 14 to 21 days of repeated 28-day cycles should be considered. Dosing should not exceed 21 days during any 28-day period. Onureg should be discontinued if more than 15% blasts are observed in either the peripheral blood or bone marrow or at the physician's discretion.

2.5.4. Conclusions on the clinical efficacy

The results of the pivotal study demonstrated a significant and clinically meaningful prolongation of survival with a corresponding delay of relapse in subjects who achieved CR/Cri following intensive chemotherapy.

Given the limited effectiveness of current maintenance treatments for patients who attain remission after intensive induction therapy and for whom HSCT is not feasible, maintenance therapy with CC-486 may represent a treatment option for this underserved patient population. Furthermore, maintaining patients in CR for as long as possible is important since occurrence of relapse is universally associated with short survival despite treatment with salvage therapy.

In some subgroups of disease-related factors, mainly patients in CRi or patients with MRD-negative after randomization, the observed benefit should be taken with care because the evidence was not so strong with a HR = 0.74 (0,45 to 1.20) for CRi subgroup and HR = 0.81 (0,59 to 1.12) for the MRD-negative subgroup.

Based upon these data, oral azacitidine may be considered as maintenance therapy for adult patients with AML who are not candidates for curative treatment with bone marrow transplant.

2.6. Clinical safety

The main focus of the safety analysis is on safety in the target population from the pivotal Study CC-486-AML-001. The overall evaluation of safety is derived from 11 clinical studies encompassing the clinical development program for CC-486 as monotherapy, including 9 haematology studies and 2 solid tumor studies. Eight studies have been completed and 3 studies are ongoing.

The ISS Safety Population included 640 subjects who took at least one dose of CC-486 as monotherapy and for whom planned treatment schedule was at least 7 days study drug per cycle. The 233 placebo-treated subjects from Study CC-486-AML-001 are also included for comparison. In order to evaluate the overall safety profile of CC-486, analyses were performed for 6 safety pools with various studies included.

- Pool 1 - AML Maintenance, includes both maintenance studies: AML-001 (post-chemotherapy maintenance) and AML-002 (post-transplant maintenance);

- Pool 2 - Myeloid Malignancies, includes all subjects with active myeloid malignancy diseases (AML, myelodysplastic syndromes [MDS], and chronic myelomonocytic leukemia [CMML]) from studies other than AML-001 and AML-002. The rationale for separating Pools 2 and 3 is that the subjects with myeloid malignancies have more suppressed bone marrows than subjects with solid tumors or lymphomas and therefore may represent different levels of risk in terms of safety of CC-486;

- Pool 3 - Solid Tumor and Lymphoma studies are included to provide additional safety data;

- Pools 4 to 6 (Pooling CC-486 300 mg starting dose by schedule). The proposed starting dose for the targeted indication (300 mg QD), has been used in multiple CC-486 studies with three schedules: 7, 14, and 21 days of each 28-day treatment cycle. All subjects treated with the 3 different schedules are included in the following pools:

  - Pool 4: 300 mg 14 days per 28-day treatment cycle (the schedule used in the pivotal study AML-001),

  - Pool 5: 300 mg 21 days per 28-day treatment cycle, and

  - Pool 6: 300 mg 7 days per 28-day treatment cycle. (Note that there are only 4 subjects in this pool)

Patient exposure

In the pivotal study, the median treatment duration was 11.6 months (range: 0.5 to 74.3 months) for the CC-486 group and 5.7 months (range: 0.7 to 68.5 months) for the placebo group. The median average daily dose was 300.0 mg in each group (range: 202.8 to 300.6 mg, CC-486 and 150.0 to 353.6 mg, placebo). The median number of treatment cycles was 12.0 (range: 1.0 to 80.0) in the CC-486 group and 6.0 (range: 1.0 to 73.0) in the placebo group.

In the pivotal study, the demographic characteristics of the safety population were well balanced between the CC-486 and placebo treatment groups. The median (range) ages were 68.0 (55, 86) and 68.0 (55, 82) years in the CC-486 and placebo group, respectively. Most subjects were between 65 and 75 years of age (60.6% CC-486, 60.9% placebo), white (91.1%, CC-486 and 84.5%, placebo) and of European descent (70.8% CC-486, 62.7% placebo). Both treatment groups were well balanced between sexes (50% male and female, CC-486; 54.5% male and 45.5% female, placebo).

In the safety population of the pivotal study, baseline disease characteristics were generally well balanced between the CC-486 and placebo groups.

Adverse events

Analyses of TEAEs, including by severity, serious TEAEs and events leading to discontinuation, dose reductions and interruptions are summarized for the pivotal study and for Safety Pools 4, 5 and 6. For Pool 2 (active myeloid malignancies regardless of dose and dosing schedule) and Pool 3 (solid tumor/lymphoma), only for analyses of all TEAEs by SOC and PT is provided.

The primary analysis of TEAEs in the ISS excludes the following adverse event PTs from the pivotal study AML-001: acute myeloid leukemia, acute myeloid leukemia recurrent, leukemia cutis, leukemia recurrent, central nervous system leukemia, and chloroma.

The discussion of adverse events focused on the target population from the pivotal study CC-486-AML-001. Data from the 6 safety pools is summarized as supportive.

Prophylaxis against infections or gastrointestinal events was permitted in the clinical studies; however, in the pivotal study and the AZA-MDS-003 study, it was not required per protocol because of the placebo-controlled nature of the study designs.

For the pivotal study CC-486-AML-001, the SOCs in which TEAEs were most commonly reported (> 50% in the CC-486 group) were Gastrointestinal Disorders (CC-486: 91.1%; placebo: 61.8%), Blood and Lymphatic

System Disorders (65.7%, 47.2%), Infections and Infestations (62.3%; 52.8%), and General Disorders and Administration Site Conditions (57.2%; 48.5%).

After adjustment for exposure (EAIR), the incidence of TEAEs per 100 subject-years remained higher in the CC-486 treatment groups than in the placebo treatment group in the SOCs of Gastrointestinal Disorders (CC-486: 539.20; placebo: 127.64), and Blood and Lymphatic System Disorders (91.81; 59.58). For the SOC of Infections and Infestations, the EAIR was lower in the CC-486 group than in the placebo group (84.80 and 94.40, respectively).

Treatment emergent adverse events in the Gastrointestinal Disorders SOC for which the frequency differed by > 2% between treatment groups were nausea (CC-486: 64.8%; placebo: 23.6%), vomiting (59.7%; 9.9%), diarrhea (50.4%; 21.5%), constipation (38.6%; 24.0%).

Other TEAEs for which the frequency differed by > 2% between treatment groups were, neutropenia (44.5%; 26.2%), thrombocytopenia (33.5%; 27.0%), fatigue (29.7%; 19.3%), anemia (20.3%; 18.0%), asthenia (18.6%; 5.6%).

In general, the most frequently reported SOCs and TEAEs across all safety pools, were the same types as those in the pivotal study with slight differences between pools. Overall, in Pool 5, the 21/28-day dosing pool in subjects with active myeloid disease, the incidences of TEAEs was higher compared to the pivotal study.

Overall, most TEAEs reported with CC-486 treatment in the pivotal study and across safety pools, were Grade 1 or 2 and these were most frequently reported in the Gastrointestinal Disorders SOC.

In the pivotal study, at least 1 Grade 3 of 4 TEAE was reported for 71.6% of subjects in the CC-486 group and 63.1% of subjects in the placebo group. The most frequently reported TEAEs (≥ 10% of subjects in the CC-486 group) were in the following SOCs: Blood and Lymphatic System Disorders (55.5% CC-486; 41.2% placebo); Infections and Infestations (20.3% CC-486; 11.6% placebo); and Gastrointestinal Disorders (14.4% CC-486; 5.6% placebo).

The most frequently reported Grade 3 or 4 TEAE preferred terms (> 10% in the CC-486 group) were neutropenia (41.1%; 23.6%), thrombocytopenia (22.5%; 21.5%), anemia (14.0%; 12.9%), and febrile neutropenia (11.4%; 7.7%).

Serious adverse event/deaths/other significant events

The focus of the discussion of AESIs is on the categories for which an imbalance between CC486 treatment and placebo was observed in the pivotal Study CC-486-AML-001. These imbalances were observed for myelosuppression, infection, and gastrointestinal AESIs.

Myelosuppression AESIs included the subcategories of neutropenia, thrombocytopenia, anemia and general myelosuppression. In the pivotal study, the most frequently reported (> 10% in the CC-486 group) AESI preferred terms (CC-486; placebo) were neutropenia (44.5%; 26.2%), thrombocytopenia (33.5%; 27.0%), anemia (20.3%; 18.0%), febrile neutropenia (11.9%; 7.7%), and leukopenia (10.6%; 8.2%). In general, these events occurred at consistent frequencies over time in both treatment groups with the highest frequencies observed in Cycle 13 and beyond.

While myelosuppression AESIs occurred more frequently with CC-486 treatment compared to placebo, these events were largely manageable with dose modifications and standard therapeutic intervention, and few events resulted in discontinuation of study therapy.

Because myelosuppression, specifically neutropenia, is a known risk of azacitidine treatment and of AML relapse, there is an increased risk of infections in this subject population.

In the pivotal study, infection AESIs of any grade occurred in 62.3% of subjects in the CC-486 group and 52.8% in the placebo group. When adjusted for time of exposure, incidence rates for these events were 84.80 per 100 person-years for the CC-486 group and 94.40 per 100 person-years for the placebo group. In general, these events occurred at increasing frequencies over time in both treatment groups with the highest frequencies observed in Cycles 13 and beyond. The 3 infection AESIs leading to death in the CC-486 group were Klebsiella sepsis, neutropenic sepsis, and sepsis.

While infection AESIs occurred in a larger percentage of subjects on CC-486 compared to placebo, exposure adjusted incidence rates were higher in placebo-treated subjects. For the most part, these infections were likely mainly due to community acquired viral type infections. These events were largely manageable with dose modifications, and few events resulted in death or discontinuation of study therapy.

Dose modifications for gastrointestinal toxicities, with specific guidance including treatment for Grade 3 or 4 diarrhoea, nausea, and vomiting, were included in the protocol of the pivotal study. The use of a serotonin receptor antagonist, such as ondansetron or other comparable medication, as an antiemetic prophylaxis was permitted; however, it was not required in the protocol because of placebo control by study design. While increased age is a factor for constipation, it may also result either from pre-treatment/post-treatment with an antiemetic or from antidiarrheal medication as part of patient management while on study.

In the pivotal study, gastrointestinal AESI of any grade occurred in 91.1% of subjects in the CC-486 group and 66.5% of subjects in the placebo group. When adjusted for time of exposure, incidence rates for these events were 570.50 per 100 person-years for the CC-486 group and 151.12 per 100 person-years for the placebo group.

The most frequently reported (> 5% in the CC-486 group) gastrointestinal AESI preferred terms (CC-486; placebo) were nausea (64.8%; 23.6%), vomiting (59.7%; 9.9%), diarrhoea (50.4%; 21.5%), constipation (38.6%; 24.0%), abdominal pain (13.1%; 6.9%), abdominal pain upper (8.9%; 5.2%), flatulence (5.5%; 1.7%), and oropharyngeal pain (5.5%; 8.2%). In general, in the CC-486 group these events occurred at the highest frequencies in Cycles 1 to 2 and decreased through Cycles 7 to 12 with increased frequencies seen in Cycles 13 or greater.

The applicant states that gastrointestinal events were largely manageable with dose modifications, few resulted in discontinuation of therapy, and none were fatal.

Laboratory findings

Clinical laboratory evaluations are presented for AML Maintenance (Pool 1: pivotal study and Study AML-002), and Pools 4 – 6. Routine laboratory monitoring included the assessment of hematology and serum chemistry. Abnormalities noted in the laboratory test results were consistent with the previously established safety profile of azacitidine and with the underlying disease and medical history of the subjects in the various safety pools. Markedly abnormal laboratory test results were infrequent and transient.

In the CC-486 group of the pivotal study, clinically significant abnormalities in hematology parameters, recorded as Grade 3 or higher laboratory values, generally occurred beyond Cycle 18, whereas Grade 3 or higher hematology values in the placebo group occurred more frequently in Cycles 7 through 12. Over time, hematology results may reflect AML relapse in addition to treatment effects.

There were no notable findings in chemistry laboratory parameters with CC-486 treatment. Overall, there were few shifts from baseline and individual clinically significant abnormalities were consistent with the diseases under study.

For the pivotal study CC486-AML-001, changes from baseline in vital signs (systolic and diastolic blood pressure, pulse rate, body temperature, and weight) were summarized by timepoint. There were no notable changes in any vital sign parameter from baseline to treatment discontinuation.

Safety in special populations

Table 21: Pivotal Study AML-001: Summary of Treatment-emergent Adverse Events by MedDRA Terms and Age Subgroups – Safety Population

MedDRA Terms	Age Subgroups (years) for CC-486			
	< 65 (N = 65) n (%)	**65 to < 75 (N = 143) n (%)**	**75 to < 85 (N = 27) n (%)**	**≥ 85 (N = 1) n (%)**
TEAE	64 (98.5)	143 (100)	27 (100)	1 (100)
Treatment-emergent SAE[a]	28 (43.1)	64 (44.8)	12 (44.4)	0
Resulting in death	2 (3.1)	9 (6.3)	2 (7.4)	0
Requiring/prolonging hospitalization	27 (41.5)	60 (42.0)	11 (40.7)	0
Life-threatening	3 (4.6)	5 (3.5)	2 (7.4)	0
Persistent/significant disability/incapacity	0	1 (0.7)	1 (3.7)	0
Other medically important event	3 (4.6)	5 (3.5)	4 (14.8)	0
TEAE leading to permanent treatment discontinuation	33 (50.8)	94 (65.7)	19 (70.4)	1 (100)
Psychiatric disorders (SOC)	12 (18.5)	20 (14.0)	10 (37.0)	0
Nervous system disorders (SOC)	18 (27.7)	52 (36.4)	11 (40.7)	0
Injury, poisoning, and procedural complications (SOC)	11 (16.9)	29 (20.3)	9 (33.3)	0
Cardiac disorders (SOC)	3 (4.6)	14 (9.8)	1 (3.7)	0
Vascular disorders (SOC)	9 (13.8)	25 (17.5)	3 (11.2)	0
Infection and infestations (SOC)	42 (64.6)	87 (60.8)	18 (66.7)	0
Cerebrovascular disorders (SMQ)[b]	0	5 (3.5)	0	0
Anticholinergic syndrome (PT)	0	0	0	0
Quality of life decreased (PT)	0	0	0	0

MedDRA Terms	Age Subgroups (years) for CC-486			
	< 65 (N = 65) n (%)	**65 to < 75 (N = 143) n (%)**	**75 to < 85 (N = 27) n (%)**	**≥ 85 (N = 1) n (%)**
Sum of postural hypotension, falls, blackouts, syncope, dizziness, ataxia, fractures[c]	8 (12.3)	32 (22.4)	5 (18.5)	0
Asthenia	8 (12.3)	28 (19.6)	8 (29.6)	0
Constipation	24 (36.9)	50 (35.0)	17 (63.0)	0
Decreased appetite	9 (13.8)	14 (9.8)	7 (25.9)	0
Insomnia	6 (9.2)	10 (7.0)	6 (22.2)	0
Pollakiuria	0	1 (0.7)	3 (11.1)	0

HLGT = High Level Group Term; HLT = High Level Term; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SAE = serious adverse event; SMQ = Standardized MedDRA Query; SOC = system organ class; TEAE = treatment-emergent adverse event

[a] Subjects may have met more than one SAE criteria.

[b] Search includes Narrow scope of Sub-SMQ Hemorrhagic central nervous system vascular conditions, Narrow scope of Sub-SMQ Ischemic central nervous system vascular conditions and Narrow scope of Sub-SMQ Conditions associated with central nervous system hemorrhages and cerebrovascular accidents.

[c] Search includes PTs of orthostatic hypotension, fall, loss of consciousness, syncope, dizziness, dizziness exertional, dizziness postural, persistent postural-perceptual dizziness, and procedural dizziness; HLT Gait disturbances and HLT Coordination and balance disturbances; and HLGT Fractures

Treatment-emergent adverse events include adverse events that started between first dose date and the date 28 days after the last dose date of study treatment

Coded using MedDRA version 22.0. A subject is counted only once for multiple events within preferred term/system organ class

Immunological events

N/A

Safety related to drug-drug interactions and other interactions

No formal clinical drug interaction studies with injectable or oral azacitidine have been conducted. Based on in-vitro data, azacitidine metabolism does not appear to be mediated by cytochrome P450 isoenzymes (CYPs); therefore, CYP inhibitors and inducers are unlikely to have any impact on the metabolism of azacitidine. Azacitidine is not a P-gp substrate or inhibitor and is unlikely to produce any clinically relevant interactions with P-gp.

Discontinuation due to adverse events

In the CC-486 and placebo groups of the pivotal study, 13.1% and 4.3% of subjects, respectively, experienced at least 1 TEAE leading to study treatment discontinuation. In the CC-486 group, TEAEs leading to treatment

discontinuation experienced by more than 1 subject were nausea (2.1% versus 0%), diarrhea (1.7% versus 0%), vomiting (1.3% versus 0%), abdominal pain upper, and fatigue (0.8% versus 0% for each).

Gastrointestinal disorders that led to treatment discontinuation occurred at a higher frequency overall (SOC: 4.7% CC-486; 5.3% Pool 1; 4.8% Pool 4; and 6.7% Pool 5) and for each preferred term in the CC-486 group compared to the placebo group (SOC: 0.4%).

In Study CC-486-AMl-001, a maximum of 1 dose reduction to a daily dose of 200 mg was permitted in the event of toxicity. In the event of continuing toxicity that did not respond to dose reduction, a maximum of 1 treatment schedule (frequency) modification from 14 to 7 days was allowed. Treatment-emergent adverse events leading to dose reduction were reported for 15.7% of subjects in the CC-486 group and 2.6% of subjects in the placebo group.

The types of TEAEs that led to dose reduction were consistent with the safety profile of azacitidine.

In the pivotal study, treatment-emergent adverse events leading to dose interruption were reported for 43.2% and 17.2%, in the CC-486 and placebo group, respectively. In general, the types of TEAEs that led to dose interruption were consistent with the safety profile of azacitidine.

Post marketing experience

Oral azacitidine is currently marketed in the US.

Post marketing experience is available for injectable azacitidine (Vidaza) and includes approximately 443,478 patients up to 18 May 2019.

Cumulatively, approximately 21,293 subjects have been treated with azacitidine in clinical studies.

During the reporting interval (19 May 2018 to 18 May 2019), potential safety signals for azacitidine of progressive multifocal leukoencephalopathy (PML), eosinophilic pneumonia (EP), and differentiation syndrome (DS) were identified and Safety Topic Reviews (STRs) were performed. Based upon these analyses, the available data did not provide enough evidence to support a causal relationship between PML, EP and DS, and azacitidine. The signals were closed and refuted. The signals evaluated and a review of all the risks during the reporting interval provided no new information requiring changes to labelling or risk mitigation.

Although the STR did not indicate a causal relationship between azacitidine and Differentiation Syndrome, following communication with the FDA, the MAA agreed to submit by 1Q 2020 a post-marketing section of the Vidaza USPI that would include Differentiation Syndrome.

Other safety information

There were 4 cases of overdose reported for subjects receiving oral azacitidine. There were no adverse events associated with the overdoses except for 1 case in which the subject reported nausea on the day of the overdose which resolved the same day.

No potential for drug dependence, misuse, or abuse have been noted for oral azacitidine in any of the clinical studies.

There is no pharmacological mechanism by which withdrawal of oral azacitidine would be expected to exert any adverse pharmacodynamic effect. There is no evidence of withdrawal effects during interruptions of oral azacitidine treatment and following cessation of oral azacitidine treatment.

No studies on the effects of oral azacitidine on the ability to drive or use machinery have been performed.

Pregnant and lactating women were excluded from the study population and throughout the clinical development program. As of the safety data cut-off date, there are no data regarding the clinical effects of injectable or oral azacitidine in pregnancy.

2.6.1. Discussion on clinical safety

In the pivotal study CC-486-AML-001, oral azacitidine showed a manageable and acceptable safety profile that is consistent with the known safety profile of azacitidine (observed with the injectable formulation).

The safety profile of oral azacitidine is primarily characterized by the gastrointestinal toxicities of nausea, vomiting, diarrhea, constipation and abdominal pain, and hematologic toxicities of neutropenia, thrombocytopenia, febrile neutropenia and leukopenia.
Most gastrointestinal events were Grade 1 or 2 in severity and were largely manageable with dose modifications, few resulted in discontinuation of therapy, and none were fatal. While neutropenia occurred more frequently with oral azacitidine treatment compared to placebo, these events were largely manageable with dose modifications and standard therapeutic intervention, few events resulted in discontinuation of study therapy and none were fatal in the pivotal study. Patients should be advised to promptly report febrile episodes. Patients with low platelet counts should be advised to report early signs or symptoms of bleeding.

Overall, adverse events of infections occurred in > 60% of oral azacitidine-treated subjects in the pivotal study and across the safety pools and in > 50% of placebo-treated subjects and were largely attributed to viral/community type infections (e.g., influenza, nasopharyngitis and pneumonia). However, individual PTs occurred in < 20% of subjects and while individual infection PTs occurred in a larger proportion of oral azacitidine -treated subjects compared to placebo, exposure adjusted incidence rates in Study CC-486-AML-001 were higher in placebo-treated subjects.

Anti-emetic and anti-diarrheal medications, GCSF and anti-infective medications should be considered (based on individual patient characteristics, treatment response and according to the current clinical guidelines) during oral azacitidine treatment as prophylaxis for treatment of gastrointestinal events, neutropenia and infections, respectively).

A PK analysis performed by the applicant seems to suggest that the occurrence of gastrointestinal AEs (i.e. nausea, vomiting, diarrhoea) do not significantly affect absorption over the first two cycles thereby decreasing the risk of reduced efficacy. Moreover, the risk of gastrointestinal AEs appears to be transient with reduced incidence after Cycle 1.

There were no adverse events associated with the overdoses reported in the clinical trials except for 1 case in which the subject reported nausea on the day of the overdose which resolved the same day. In the event of overdose, the patient should be monitored including appropriate blood counts and should receive supportive treatment, as necessary. There is no known specific antidote for azacitidine overdose. See Section 4.9 of the SmPC.

There are no adequate data from the use of Onureg in pregnant women. Studies in mice and rats have shown reproductive and developmental toxicity (see Non-Clinical section). The potential risk for humans is unknown. Based on results from animal studies and its mechanism of action, women of childbearing potential receiving azacitidine should be advised to avoid pregnancy and use effective contraception during treatment and up to 6 months after treatment. Male patients receiving azacitidine should be advised to use effective contraception up to 3 months after the last dose of oral azacitidine.

2.6.2. Conclusions on the clinical safety

Given the extensive experience from injectable azacitidine, the safety profile of the oral product seems fairly well established and the main adverse effects are gastrointestinal and hematologic toxicities.

The incidence of gastrointestinal toxicities appears to be higher with the oral formulations as compared with the parenteral formulation.

2.7. Risk Management Plan

Safety concerns

The RMP version 15.4, dated 15 March 2021includes the following safety concerns:

Table 22: Summary of safety concerns for Oral azacitidine

Important identified risks	Infections
Important potential risks	None
Missing information	None

Pharmacovigilance plan

Routine pharmacovigilance is considered sufficient to identify and characterise the risks of the product.

Risk minimisation measures

Routine risk minimisation measures are considered sufficient to minimise the risks of the product.

Conclusion

The CHMP and PRAC considered that the risk management plan version 15.4 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

Based on the fact that Onureg involves a new route of administration and the indication, posology and dosing schedule differ from the azacitidine for injection, the CHMP is of the opinion that a separate entry in the EURD list for oral azacitidine is needed. The new entry for oral azacitidine should have a PSUR submission cycle of 1 year.

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request the alignment of the new PSUR cycle with the international birth date (IBD). The IBD is 19 May 2004. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Onureg is indicated as maintenance therapy in adult patients with acute myeloid leukaemia (AML) who achieved complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following induction therapy with or without consolidation treatment and who are not candidates for, including those who choose not to proceed to, hematopoietic stem cell transplantation (HSCT).

3.1.2. Available therapies and unmet medical need

The usual treatments for newly diagnosed AML patients without serious comorbidities include intensive chemotherapy to induce remission (induction chemotherapy). Intensive induction chemotherapy typically consists of cytarabine in combination with an anthracycline. In order to deepen the level of remission through eradication of residual leukemia, patients typically receive consolidation chemotherapy. There is no consensus regarding the optimal approach to the number of cycles of consolidation therapy.

The therapeutic approaches for patients who can tolerate intensive therapy are usually divided into two phases: induction of remission and post-remission (consolidation) therapy. Although patients can achieve CR and disease control after induction, patients who do not receive post remission consolidation therapy are more likely to relapse, usually within 6 to 9 months. Post remission therapy is recommended for patients younger than 60 years old and for older patients who are fit for intensive therapy.

For patients who cannot tolerate intensive induction therapy, combinations of low intensity therapy with novel agents such as venetoclax and glasdegib has shown improved responses and/or survival.

Allogeneic HSCT is the only potentially curative treatment for patients with AML. However, HSCT is not a feasible treatment option for many patients, and the frequency of patients undergoing HSCT decreases with increasing age due to the increased prevalence of comorbidities and poor organ function limiting the benefit-risk assessment of the procedure. Despite treatment with consolidation chemotherapy, and even HSCT, relapse rates after these therapies remain high and contribute to the poor outcomes in AML. Salvage therapy following relapse is limited, particularly for patients who are not candidates for transplant. Intensive chemotherapy can offer the highest CR rates; however, its application is limited by tolerability, in particular, the high treatment-related mortality and short remission duration.

Maintenance therapy conducive to long-term tolerable drug administration could potentially prolong remission and survival in the post-consolidation setting, particularly in those with intermediate risk and high-risk disease as well as those who do not proceed to transplant. Despite the approval of Ceplene (histamine dihydrochloride) and Rydapt (midostaurin) in some countries as a maintenance therapy for AML, given the lack of convincing benefit (eg, prolonging survival, Dohner, 2017), maintenance therapy with these agents is globally not considered standard of care. Effective maintenance therapy could provide an important therapeutic approach to treatment of patients with AML, a disease associated with short survival and a high unmet medical need.

Current salvage therapy at time of relapse is inadequate, particularly for subjects not eligible for transplant. Duration of first Complete Remission (CR) is an important predictor of outcome, with longer duration of first CR associated with better survival. Therefore, maintaining patients in CR is an important therapeutic goal in AML. As most patients will relapse, effective maintenance treatment for patients who do attain remission may play a role in preventing relapse and prolonging OS, especially in those for whom HSCT is not feasible.

Azacitidine is an analogue of the naturally occurring pyrimidine nucleoside cytidine and is classified as an antimetabolite. Vidaza, the injectable formulation of the same active ingredient azacitidine, is considered a standard of care for patients with AML who are ineligible to receive intensive chemotherapy globally. Vidaza (Azacitidine for Injection), is approved in the European Union (EU) for the treatment of adult patients who are not eligible for hematopoietic stem cell transplant (HSCT) with:

- intermediate-2 and high-risk MDS according to the International Prognostic Scoring System (IPSS),
- chronic myelomonocytic leukaemia (CMML) with 10-29% marrow blasts without myeloproliferative disorder,
- acute myeloid leukemia (AML) with 20-30% blasts and multi-lineage dysplasia, according to WHO classification,
- AML with >30% marrow blasts according to the World Health Organization (WHO) classification.

The oral form of azacitidine was developed to allow sustained and extended administration of azacitidine at lower systemic doses than can be practically achieved with parenteral therapy. It is expected that an oral formulation can be administered in outpatient settings and could provide a more convenient route of administration for patients. The risk of recurrent injection site reactions observed when azacitidine is administered by the SC route could be reduced with the oral formulation.

3.1.3. Main clinical studies

The clinical package of Onureg was primarily supported by the pivotal Phase 3 placebo-controlled study (Study CC- 486-AML-001). Study CC- 486-AML-001 was a Phase 3, double-blind, randomized, placebo-controlled, multicenter study designed to compare the efficacy and safety of oral azacitidine plus BSC (n=238) vs placebo plus BSC (n=234) as maintenance therapy in subjects who achieved CR/CRi after induction with intensive chemotherapy with or without consolidation. Subjects with CR/CRi after treatment with hypomethylating agents (HMAs), subjects with good risk cytogenetics, and those who were candidates for HSCT were excluded.

3.2. Favourable effects

In study CC- 486-AML-001, the median OS was 24.7 months for the oral azacitidine group vs 14.8 months for the placebo group after a median follow-up time of 41.2 months based on reverse Kaplan-Meier method, with a clinically meaningful difference in median OS of 9.9 months with CC-486 treatment. The hazard ratio (HR) was 0.69 (95% confidence interval [CI]: 0.55, 0.86), indicating a 31% reduction in the risk of death for the oral azacitidine group.

The median RFS was 10.2 months for the oral azacitidine group vs 4.8 months for the placebo group, in median RFS of 5.3 months with oral azacitidine treatment. The HR was 0.65 (95% CI: 0.52, 0.81), indicating a 35% reduction in risk of relapse or death for the oral azacitidine group. A lower death rate was observed in the oral azacitidine group compared with the placebo group as early as 90 days after randomization (4 [1.7%] subjects versus 20 [8.5%] subjects, respectively).

The proportion of subjects surviving at the 1-year time point was 72.8% in the oral azacitidine group vs 55.8% in the placebo group, for a difference of 17.0%. The proportion of subjects surviving at the 2-year time point was 50.6% in the oral azacitidine group vs 37.1% in the placebo group, for a difference of 13.5%.

The probability of RFS at the 6-month time point was 67.4% in the oral azacitidine group vs 45.2% in the placebo group, for a difference of 22.2%. The probabilities of RFS were consistently higher for the oral azacitidine group than for the placebo group at each of the later time points (44.9% versus 27.4%, respectively, at 1 year and 26.6% versus 17.4% at 2 years), demonstrating durable efficacy over time for oral azacitidine treatment. Sensitivity analyses of OS and RFS provided support for the robustness and consistency of the results of the primary and key secondary efficacy endpoints.

Study CC-486-AML-001 also demonstrated that subjects receiving oral azacitidine, compared with those receiving placebo, had significantly lower rates of hospitalization events (0.48 events per person-year for the CC-486 group and 0.64 events per person-year for the placebo group; nominal $p = 0.0068$) and number of days hospitalized (7.89 days per person-year for CC-486 compared with 13.36 day per person-year for placebo; nominal $p < 0.0001$).

The results for the secondary endpoints corroborated the results seen with the primary endpoint.

Study AZA-MDS-003 is considered supportive of the efficacy results for oral azacitidine. The primary efficacy endpoint of RBC-TI with duration ≥ 56 days (8 weeks) in the ITT population was achieved in 31% of subjects in the oral azacitidine treatment group compared with 12% of subjects in the placebo treatment group, with a statistically significant difference of almost 19% ($p = 0.0005$). The median duration of RBC-TI among subjects in the CC-486 treatment group who achieved RBC-TI for at least 56 days was 11.1 months with a median onset of 2.4 months. The rate of achieving RBC-TI with duration ≥ 84 days (12 weeks) was significantly higher in the oral azacitidine treatment group compared with the placebo treatment group (28.0% versus 6.4%,

respectively; $p < 0.0001$). The median duration of RBC-TI and the median onset are consistent with the results of RBC-TI of ≥ 56 days.

3.3. Uncertainties and limitations about favourable effects

In the pivotal study CC-486-AML-001, a 9.9-month improvement in median OS in the oral azacitidine treatment was reached, compared to placebo. After 48 months, the survival probability was very close to each other in both arms and the Kaplan-Meier curves were almost overlapping from 64 months onwards. The updated OS data from 15 Oct 2019 and 20 Sep 2020 (providing 3 and ~14 additional months of follow-up, respectively) and RFS data from 15 Oct 2019 (3 additional months of follow-up) are consistent with the results from the earlier data cut off (15 Jul 2019) reported in the CSR, with unchanged median OS and RFS and HR with additional follow-up, demonstrating the robustness of the results. Furthermore, the tail end of the updated OS and RFS curves showed increased separation compared with those from the earlier data cut off provided in the CSR. It is agreed that the updated data support the original conclusion that oral azacitidine maintenance therapy has significant impact on survival and delay of relapse in subjects who achieved CR/CRi following intensive chemotherapy.

One of two amendments introduced to the protocol CC-486-AML-001 concerned the modification of the Inclusion Criterion #4 to change the amount of time required for subjects to be in complete remission (CR) or in complete remission with incomplete blood count recovery (CRi) from 3 months to 4 months (± 7 days). This amendment had the potential to increase the number of patients included in the trial with best prognostic factors, that were able to maintain the response for a long period of time. However, in the applicant's opinion this effect would not influence the final results of the study, because the randomization would be a guarantee that the proportion of patients with better prognosis would be balanced between both arms. The explanation provided in the applicant's response is considered acceptable, although such amendments to the protocol can be considered as a limitation of the clinical trial.

In the subgroup analysis, it appears that only in European population the effect of oral azacitidine was favourable. The Applicant performed additional analyses that showed that regional or racial differences in the OS and RFS benefit associated with CC-486 treatment were likely due to larger variability caused by small sample size.

Although it has been shown that in the population of subjects aged ≥ 65 years suffering from newly diagnosed AML with a BM blast count > 30% and not eligible for HSCT, treatment with azacitidine resulted in a median OS of 10.4 months, a clinically meaningful increase of 3.8 months over CCR with an increase of 12.3% in the 1-year survival estimate over CCR, and the primary OS analysis did not meet the conventional level of statistical significance.

It would have been expected that the final results of the supportive Study AZA-MDS-003 could provide confirmatory support of the efficacy and safety of oral azacitidine. However, the primary objective of the trial was not related to OS or RFS. The objective was to evaluate RBC Transfusion Independence (RBC-TI) in each of the 2 treatment groups (oral azacitidine versus placebo) in subjects with RBC transfusion-dependent anemia and thrombocytopenia due to IPSS lower-risk MDS. However, subjects were treated for vitamin B12 deficiency. This makes the interpretation of the interim results difficult.

The extension of the treatment after relapse from 14 to 21 days of oral azacitidine in the experimental arm was limited to a small number of patients and thus it is difficult to determine the effect of the treatment extension. Nevertheless and especially since there are no safety concerns identified with this treatment

extension of the dosing schedule from 14 to 21 days, in the case of disease relapse in patients with 5% to 15% blasts in peripheral blood or bone marrow, such an extension of the dosing schedule should be considered, in conjunction with a clinical assessment.

3.4. Unfavourable effects

Gastrointestinal toxicities

Incidence in the pivotal trial: ~92% in the oral azacitidine group.

Symptoms: nausea, vomiting, diarrhoea, and constipation.

Hematologic toxicities

Incidence in the pivotal trial: ~66% in the CC-486 group.

Symptoms: neutropenia (leading to an increased risk of infections), thrombocytopenia and anemia.

Among AEs grade 3 and 4 Blood and Lymphatic System Disorders in addition to Infections and Infestations were most commonly reported.

Blood and Lymphatic System Disorders and Gastrointestinal Disorders were reasons for dose reduction and dose interruption.

Myelosuppression AESIs occurred at consistent frequencies over time in both treatment groups with the highest frequencies observed in Cycle 13 and beyond.

3.5. Uncertainties and limitations about unfavourable effects

The clinical safety of oral azacitidine is based on the results of 640 subjects who took at least one dose of azacitidine in 11 different clinical trials. The number of patients is considered rather limited.

In the study CC-486-AML-001, the lower exposure of the placebo group is related to the earlier relapse of the disease with suspension of treatment and could influence the safety results.

The baseline hematologic values, namely hemoglobin, absolute neutrophil count and platelets, are affected by the previous treatment with high dose chemotherapy, as a consequence the abnormal haematological finding may be not totally drug related.

Upon stratification of the studied population it is possible to observe that patients ≥ 75 years old experienced higher rates of TEAEs leading to drug interruption. Even so, any decision to restricted the indication or strengthen the monitoring in these age group has to be taken cautiously considering the small number of subjected included (28 and 23 subjects for treatment and placebo arms, respectively vs. 143 and 142 for patients between ≥ 65 to < 75 yrs). It should be noted, however, that the safety profile of azacitidine in this population is as expected.

TEAEs were comparable between racial groups for most categories and no discernible effect of race was observed. However, the number of Asian, black or other racial groups in the oral azacitidine studies were small and comparisons cannot be made between racial subgroups.

No formal clinical drug-drug interaction studies with injectable or oral azacitidine have been presented.

The high incidence of gastrointestinal toxicities introduces some uncertainty as regards patient compliance outside a trial and bioavailability of azacitidine when compared to SC administration.

3.6. Effects Table

Table 23: Effects Table for ONUREG (oral azacitidine) as maintenance therapy in adult patients with acute myeloid leukaemia (AML) who achieved complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following induction therapy with or without consolidation treatment and who are not candidates for, including those who choose not to proceed to, hematopoietic stem cell transplantation (HSCT) (data cut-off: 15 July 2019).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Overall survival	Number of deaths	n (%)	158 (66.4)	171 (73.1)	SoE: Hazard ratio C/P (95% CI) 0.69 (0.55, 0.86), p=0.0009	CC-486-AML-001
	Median overall survival	(months) (95% CI)	24.7 (18.7, 30.5)	14.8 (11.7, 17.6)	SoE: Hazard ratio C/P (95% CI) 0.69 (0.55, 0.86), p=0.0009	
Relapse-free Survival	Number of relapsed or died	n (%)	164 (68.9)	181 (77.4)	SoE: Hazard ratioC/P (95% CI) 0.65 (0.52, 0.81), p=0.0001	CC-486-AML-001
	Median relapse-free survival	months (95% CI)	10.2 (7.9, 12.9)	4.8 (4.6, 6.4)	SoE: Hazard ratioC/P (95% CI) 0.65 (0.52, 0.81), p=0.0001	
Time to Relapse	Subjects relapsed	n (%)	154 (64.7)	179 (76.5)	SoE	CC-486-AML-001
Time to Treatment Discontinuation	Median time to treatment discontinuation	months[e] (95% CI)	11.4 (9.8, 13.6)	6.1 (5.1, 7.4)	SoE	CC-486-AML-001
Unfavourable Effects						
Nausea	Incidence of nausea	%	64,8	23,6		
Vomiting	Incidence of vomiting	%	59,7	9,9		
Diarrhoea	Incidence of diarrhoea	%	50,4	21.5		

Notes:
1) Pivotal study CC-486-AML-001
CI = confidence interval; C/P = CC-486/placebo; ITT = intent-to-treat.
[a] Median estimate of OS and RFS is from an unstratified Kaplan-Meier analysis.
[b] The hazard ratio is from a Cox proportional hazards model stratified by age, cytogenetic risk category, and received consolidation therapy or not.
[c] The p-value is 2-sided from a log-rank test stratified by age, cytogenetic risk category, and received consolidation therapy or not.
[d] Unstratified Kaplan-Meier analysis

[e] Median estimate of time to discontinuation is from an unstratified Kaplan-Meier analysis.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The results of the pivotal study demonstrated a statistically significant and clinically meaningful prolongation of survival with a corresponding delay of relapse in subjects who achieved CR/Cri following intensive chemotherapy. A 9.9-month improvement in median OS and a 5.4 months median relapse-free survival in the oral azacitidine treatment was reached, compared with the placebo. Other secondary endpoints (time to relapse and time to discontinuation from treatment) as well as health related quality of life measurements were also supportive of the demonstrated benefit of oral azacitidine as maintenance therapy for the treatment of AML.

Given the limited options for maintenance treatment for patients who attain remission after intensive induction therapy and for whom HSCT is not feasible, maintenance therapy with oral azacitidine may represent a treatment option for this underserved patient population. Furthermore, maintaining patients in CR for as long as possible is important since occurrence of relapse is universally associated with short survival despite treatment with salvage therapy.

In the pivotal trial essentially all patients (92%) in the oral azacitidine arm experienced gastrointestinal toxicities (e.g. nausea, vomiting, diarrhoea). Although these events appeared to be manageable, they were also an important reason for discontinuations and dose reductions / interruptions.

The high incidence of gastrointestinal toxicities introduces uncertainty as regards patient compliance outside a trial and bioavailability of azacitidine when compared to SC administration. Hence, increased convenience of oral administration risks being offset by lower compliance and a more variable and unpredictable absorption potentially increasing the risk of AML relapse.

3.7.2. Balance of benefits and risks

Given the clinical relevance and statistically significant results of the pivotal study, the benefit/risk balance of oral azacitidine can be considered favourable.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Onureg is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Onureg is not similar to Dacogen, Rydapt, Mylotarg, Vyxeos liposomal, Xospata and Daurismo within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Onureg is favourable in the following indication:

Onureg is indicated as maintenance therapy in adult patients with acute myeloid leukaemia (AML) who achieved complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following induction therapy with or without consolidation treatment and who are not candidates for, including those who choose not to proceed to, hematopoietic stem cell transplantation (HSCT).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being

received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

Appendix

1. CHMP AR on similarity dated 22 April 2021