CENTER FOR DRUG EVALUATION AND RESEARCH

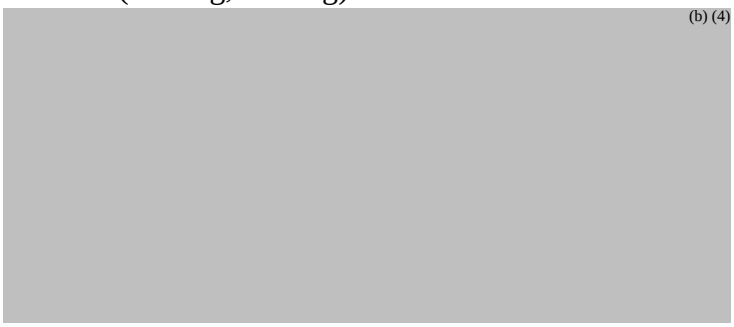
APPLICATION NUMBER:

214120Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA Multidisciplinary Review and Evaluation

Application Number	**NDA 214120**
Application Type	Type 3
Priority or Standard	Priority
Submit Date	3/3/2020
Received Date	3/3/2020
PDUFA Goal Date	9/3/2020
Office/Division	OOD/DHM1
Review Completion Date	9/1/2020
Applicant	Celgene Corporation
Established Name	Azacitidine
(Proposed) Trade Name	Onureg
Pharmacologic Class	Nucleoside metabolic inhibitor
Formulations	Tablet (200 mg, 300 mg)
Applicant Proposed Indication/Population	(b) (4) 
Recommendation on Regulatory Action	Regular approval
Recommended Indication/ Population	For continued treatment of adult patients with acute myeloid leukemia who achieved first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following intensive induction chemotherapy and are not able to complete intensive curative therapy.
SNOMED CT for the Recommended Indication/Population	91861009
Recommended Dosing Regimen	300 mg orally daily on Days 1 through 14 of each 28-day cycle

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GLOSSARY

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice

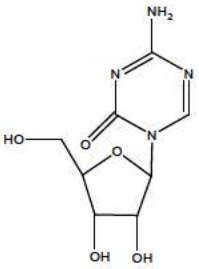
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report PDpharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy SAEserious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 EXECUTIVE SUMMARY

1.1 PRODUCT INTRODUCTION

Proposed Trade Name:	Onureg®
Established Name:	Azacitidine
Also Known As:	CC-486, 5-azacitidine
Chemical Name:	4-amino-1-β-D-ribofuranosyl-s-triazin-2(1H)-one
Molecular Formula:	$C_8H_{12}N_4O_5$
Molecular Weight:	244 g/mol
Dosage Forms:	Tablet (200 mg, 300 mg)
Therapeutic Class:	Antineoplastic
Chemical Class:	Small molecule
Pharmacologic Class:	Nucleoside metabolic inhibitor
Mechanism of Action:	Azacitidine is a pyrimidine nucleoside analog of cytidine that inhibits DNA and RNA methyltransferase.

Chemical Structure:



NDA 214120 for Onureg was submitted under the 505(b)(1) pathway for the indication (b) (4)

[redacted]

1.2 CONCLUSIONS ON THE SUBSTANTIAL EVIDENCE OF EFFECTIVENESS

The review team recommends regular approval of azacitidine tablets under 21 CFR 314.105 for the indication "for continued treatment of adult patients with acute myeloid leukemia who achieved first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following intensive induction chemotherapy and are not able to complete intensive curative therapy" using a dose of 300 mg orally on Days 1-14 of a 28-day cycle. The recommendation is based on improvement in overall survival (OS) in Study CC-486-AML-001 (QUAZAR; NCT01757535).

Appropriate dosing for patients with moderate or severe hepatic impairment remains to be determined in postmarketing studies.

Study CC-486-AML-001 was a multicenter, randomized, double-blind, placebo-controlled study. Eligible patients were ages 55 years or older, had acute myeloid leukemia (AML), and were within 4 months of achieving first CR or CRi with intensive induction chemotherapy. Patients may have received consolidation, but patients were excluded if they were candidates for hematopoietic stem cell transplantation (HSCT) at the time of screening.

Patients were randomized 1:1 to receive azacitidine tablets 300 mg (n=238) or placebo (n=234) orally on Days 1 - 14 of each 28-day cycle. The azacitidine dose was based on tolerability in other populations; no dose-ranging study was performed to select the dose to be tested in this intended population. Randomization was stratified by age at time of induction therapy (55 to 64 years vs. ≥ 65 years), cytogenetic risk category at time of induction therapy (intermediate risk vs. poor risk), prior history of myelodysplastic syndrome or chronic myelomonocytic leukemia (MDS/CMML) (yes vs. no), and received consolidation therapy following induction therapy (yes vs. no).

There were 472 patients randomized to treatment with azacitidine tablets (n=238) or placebo (n=234). The study arms were balanced for key demographic and disease characteristics. The randomized population had a median age of 68 years (range, 55-86 years), 52% were male, 88% were White, 7% were Hispanic, and 17% were from North America. ECOG performance status was 0 or 1 for 92%. AML at diagnosis had intermediate risk cytogenetics for 86% and poor risk for 14%, and 91% had de novo AML. The median time from induction response to randomization was 85 days (range 7, 263); 20% had received no consolidation, 45% 1 cycle of consolidation, 31% 2 cycles of consolidation, and 4% 3 cycles of consolidation. At the time of study baseline, 78% were in CR, 17% in CRi and 5% neither CR nor CRi.

The primary endpoint of Study CC-486-AML-001 was OS. Assuming a median OS of 16 months in the placebo arm and 22.9 months in the azacitidine arm, and a study duration of 60 months, 330 events among 460 subjects (230 per treatment arm) would be needed to achieve at least 90% power to detect a significant difference in OS with a hazard ratio (HR) of 0.70. As of the 7/15/2019 data cut, there were 329 events among the 472 randomized patients. The median follow-up on study was 11.9 (range, 1.1, 62.5) months. There was a significant difference between arms in OS (HR 0.69; 95% CI 0.55, 0.86; p=0.0009); the median OS was 24.7 months in the azacitidine arm and 14.8 months in the placebo arm. The results were concluded to be consistent on subgroup analysis and did not appear to be impacted by poststudy therapy.

Some uncertainty was raised by the fact that there was only a single trial, and it was for treatment of patients largely without overt disease for whom a direct effect on the leukemia could not be measured. The Applicant did provide minimal residual disease data (MRD), but the MRD assay was not validated for the threshold needed to make conclusions, so the results were not considered credible. The parenteral formulation of azacitidine has established efficacy in combination with venetoclax for treatment AML, but azacitidine tablets have a very different bioavailability in comparison to the parenteral formulation, so antileukemia activity of the oral formulation could not be inferred from those data. The concern was allayed somewhat

by the observation of biological antileukemia activity of azacitidine tablets in additional single-arm trials that included patients with overt AML.

Thus, the OS results of Study CC-486-AML-001 was considered substantial evidence of efficacy for treatment of adult patients with acute myeloid leukemia who achieved first CR or CRi following intensive induction chemotherapy and are not able to complete intensive curative therapy. Based on the biology of AML, this efficacy outcome can be extrapolated to the full adult age range with the condition indicated in the intended population.

1.3 BENEFIT-RISK ASSESSMENT

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Nearly all patients with AML with intermediate- and poor-risk cytogenetics will relapse after induction if not provided intensive consolidation and HSCT.	AML not treated with curative therapy is a fatal disease.
Current Treatment Options	• There are no approved drugs for patients who start intensive curative therapy for AML but who are not able to complete such treatment.	Treatment options are needed for patients not able to complete curative therapy for AML.
Benefit	• In Study CC-486-AML-001 (QUAZAR), 472 patients with AML not able to complete curative therapy were randomized 1:1 to oral azacitidine 300 mg or placebo Days 1-14 of 28-day cycles. • At study baseline, 78% had CR, 17% CRi and 5% not CR or CRi. • OS was significantly better in the azacitidine arm (HR 0.69; 95% CI 0.55, 0.86; p=0.0009) (median OS 24.7 months in the azacitidine arm and 14.8 months in the placebo arm).	There is substantial evidence that oral azacitidine improves survival in patients with AML not able to complete curative therapy.
Risks and Risk Management	• The main safety population included 236 patients treated with oral azacitidine in Study CC-486-AML-001. • The most common (≥ 10%) adverse reactions were nausea, vomiting, diarrhea, fatigue/asthenia, constipation, pneumonia, abdominal pain, arthralgia, decreased appetite, febrile neutropenia, dizziness, and pain in extremity. • There was one fatal adverse reaction (sepsis). • Adverse reactions resulted in dose interruptions in 35%, dose reductions in 14%, and discontinuation in 8%. • Grade 3-4 neutropenia occurred in 49%; grades 3-4 thrombocytopenia occurred in 21%. • AZA-MDS-003, a randomized trial using oral azacitidine 300 mg or placebo Days 1-21 of 28-day cycles, was terminated due to increased early mortality in the azacitidine arm. The most frequent fatal adverse reaction was sepsis. • The PK parameters of oral azacitidine differ substantially from those of other azacitidine formulations; substitutions between formulations pose a risk for harm. • The exposure and safety of oral azacitidine has not been studied in patients with moderate or severe hepatic impairment.	The safety profile of azacitidine tablets is acceptable for the intended population. The major potential risks can be mitigated through labeling, including notice of class-specific risks. Studies are needed to establish a safe dose in patients with hepatic impairment.

Patients with AML who respond to standard intensive induction but are not able to complete curative therapy have a poor prognosis. The results of Study CC-486-AML-001 showed that treatment with oral azacitidine conferred a clinically meaningful improvement in OS in comparison to placebo (HR 0.69; 95% CI 0.55, 0.86; p=0.0009; median OS 24.7 months vs 14.8 months, respectively) in this patient population. Although Study CC-486-AML-001 was limited to patients age 55 years or older, based on the biology of AML, this efficacy outcome can be extrapolated to the full adult age range with the condition indicated in the intended population.

In general, the safety profile of oral azacitidine is as expected for a cytotoxic drug. In Study CC-486-AML-001, fatal adverse reactions were limited by monitoring and dose modifications that can be used in labeling. One potential shortcoming is the relatively small safety database in comparison to the potential intended population. As the active ingredient is the same as in the parenteral formulation, class-specific risks identified for the parenteral formulation, including hypersensitivity, should also be included in labeling to address this shortcoming.

The safety experience also included results from Study AZA-MDS-003, randomized, double-blind, placebo-controlled trial comparing azacitidine 300 mg or placebo Days 1-21 of 28-day cycles. Enrollment was discontinued early due to a higher incidence of early fatal and/or serious adverse reactions in the oral azacitidine arm. It is not clear whether this adverse safety profile was due to the extended dosing of oral azacitidine or to factors intrinsic to the MDS population, but since either would pose a risk to the public health, the results should be described in a warning in labeling.

It was also noted that the PK parameters of oral azacitidine differ substantially from those of other azacitidine formulations, and the recommended dose and schedule are different from those for the intravenous or subcutaneous azacitidine products; hence, substitutions between formulations pose a substantial risk for harm. This risk can be described adequately in a warning in labeling.

Lastly, the effect of moderate or severe hepatic impairment on azacitidine exposure and safety has not been studied. A postmarketing clinical study will be needed to identify a safe oral azacitidine dose in patients with moderate and severe hepatic impairment.

Given the observed survival improvement, and with adequate labeling in place to mitigate risks, the clinical benefit of oral azacitidine appears to outweigh the risks for adult patients with acute myeloid leukemia who achieved first CR or CRi following intensive induction chemotherapy and are not able to complete intensive curative therapy.

1.4 PATIENT EXPERIENCE DATA

Patient Experience Data Relevant to this Application

☒	The patient experience data that was submitted as part of the application, include:				Section where discussed
	☒	Clinical outcome assessment (COA) data, such as			
			☒	Patient reported outcome (PRO)	8.1.1, 8.2.1, 8.3.7
			□	Observer reported outcome (ObsRO)	
			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	□	Patient-focused drug development or other stakeholder meeting summary reports			
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	□	Patient preference studies (e.g., submitted studies or scientific publications)			
	□	Other: (Please specify)			
□	Patient experience data that was not submitted in the application, but was considered in this review.				
	□	Input informed from participation in meetings with patient stakeholders			
	□	Patient-focused drug development or other stakeholder meeting summary reports			
	□	Observational survey studies designed to capture patient experience data			
	□	Other: (Please specify):			
□	Patient experience data was not submitted as part of this application.				

2 THERAPEUTIC CONTEXT

2.1 ANALYSIS OF CONDITION

Acute myeloid leukemia (AML) is the second most common form of leukemia in adults, making up approximately one third of adult leukemia cases. In the United States, approximately 20,000 new cases of AML are estimated to occur in 2020 with an estimated 11,000 deaths (American Cancer Society, 2020). Improvements in hematopoietic stem cell transplantation (HSCT) and supportive care have decreased treatment-related mortality, but relapse continues to be the most significant cause of treatment failure. Relapse and survival rates vary widely depending on numerous factors including genetic features of the disease and the intensity of initial therapy.

For patients with newly-diagnosed AML who are able to tolerate intensive therapy, standard frontline treatment typically involves induction with 7 days of cytarabine and 3 days of an

anthracycline, or what is commonly referred to as the "7+3" regimen. Complete remission (CR) rates range from 40% to 60% in older adults and 60% to 80% in younger adults (Dohner, 2017). However, it has long been recognized that after achieving first CR, nearly all patients relapse in the absence of further treatment (Cassileth, 1988) and therefore additional postremission therapy is required to prevent AML relapse. Prior randomized studies of maintenance versus consolidation showed that proceeding directly to maintenance therapy after induction resulted in worse outcomes, establishing intensive consolidation as an integral part of frontline AML therapy in patients in all age groups (Cassileth, 1992; Schlenk, 2006). Therefore, intensive post-remission therapy for AML consists of consolidation and/or, for patients with intermediate or high-risk disease, allogeneic HSCT.

Use of allogeneic HSCT is associated with the lowest rate of AML relapses and better overall survival than consolidation with chemotherapy alone or autologous HSCT for patients with intermediate- and poor-risk AML (Koreth, 2009; Yanada, 2005), but allogeneic HSCT has historically been associated with higher treatment-related morbidity and mortality (TRM). However, the incidence of TRM has decreased markedly over the past decades, and more older patients are undergoing allogeneic HSCT. Data from the Center for International Blood and Marrow Transplant Research show that the proportion of patients ≥ 70 years old undergoing transplantation in the US has increased considerably since 2000 with AML representing the most common disease indication (Muffly, 2017). Several studies have shown that allogeneic HSCT with reduced intensity conditioning in older patients has superior survival outcomes compared to conventional chemotherapy in CR1 (Estey, 2007; Mohty, 2005; Kurosawa; 2011). Thus, age alone should not preclude use of allogeneic HSCT for AML consolidation. For patients who are unable or unwilling to undergo HSCT, completion of intensive consolidation is needed to prevent relapse.

Trials reporting some measure of benefit with maintenance-type therapy have largely consisted of populations who received suboptimal induction and consolidation (Rashidi, 2016; Molica, 2019; Wei, 2019). Thus far, randomized trials have not shown that the addition of maintenance after intensive induction and consolidation confers additional benefit (Mandelli 1992; Miyawaki, 2005). Therefore, the role of maintenance in patients with AML who achieved CR1 and completed intensive induction and consolidation is unclear and requires further study. There are no approved drugs or standard treatment regimens for maintenance therapy in AML.

In the United States, standard intensive consolidation consists of 3 to 4 cycles of high-dose cytarabine (HiDAC) (Mayer, 1994). There has been debate as to the number of cycles of consolidation required, especially in the older population. Nevertheless, data suggest that patients who receive more postremission therapy appear to do better than those who receive less therapy. Even in older patients, the recent ASH guidelines note that treatment with antileukemic therapy demonstrates a survival benefit over best supportive care, and for those patients suitable for intensive therapy, the panel suggests intensive over less-intensive induction and recommends additional postremission therapy for those who are not suitable for allogeneic HSCT (Sekeres, 2020). However, a subset of patients may be unable to complete

intensive curative therapy due to on-going toxicity or other comorbid conditions.

2.2 Analysis of Current Treatment Options

There are no approved drugs for patients with AML who respond to intensive induction chemotherapy but who are not able to complete intensive consolidation with or without allogeneic HSCT, and there is no established standard of care treatment for these patients.

3 REGULATORY BACKGROUND

3.1 U.S. Regulatory Actions and Marketing History

Oral azacitidine is not marketed in the United States.

3.2 Summary of Presubmission/Submission Regulatory Activity

The key US presubmission regulatory activities for this submission are as follows:

September 11, 2006	Pre-IND written comments provided to Applicant
December 27, 2006	IND submitted
June 26, 2007	Fast track granted for azacitidine for the treatment of MDS
March 7, 2008	Pharmion Corporation acquired by Celgene Corporation
June 18, 2008	Orphan Designation granted for azacitidine for the treatment of AML (No. 08-2570)
September 6, 2011	EOP1/2 meeting
June 8, 2012	Type B meeting to discuss the design of CC-486-AML-001
September 18, 2012	Special Protocol Assessment (SPA) granted for CC-486-AML-001
December 13, 2013	SPA modification agreement – Canada country-specific protocol amendment
January 24, 2019	SPA modification – amended to add extension phase; extension phase will not affect primary efficacy analysis and patients still alive should be censoring prior to extension phase
November 21, 2019	Pre-NDA meeting
March 3, 2020	NDA 214120 submitted to FDA

4 SIGNIFICANT ISSUES FROM OTHER REVIEW DISCIPLINES PERTINENT TO CLINICAL CONCLUSIONS ON EFFICACY AND SAFETY

4.1 OFFICE OF SCIENTIFIC INVESTIGATIONS

The Office of Scientific Investigations (OSI) conducted an audit of the Applicant. OSI concluded that the Applicant appeared to be in compliance with Good Clinical Practice, and that clinical trial oversight and monitoring appeared to be adequate.

On-site inspections were planned for clinical sites 902 and 500, which enrolled the largest number of subjects on the pivotal trial CC-486-AML-001. Due to COVID-19 pandemic, these inspections could not be performed.

4.2. PRODUCT QUALITY

Onureg (azacitidine tablet) drug product is presented as film-coated tablets containing 200 mg or 300 mg of azacitidine. Each core tablet contains the following inactive ingredients: croscarmellose sodium, magnesium stearate, mannitol, and silicified microcrystalline cellulose. The 200 and 300 mg tablet coating contains hypromellose, lactose monohydrate, polyethylene glycol, titanium dioxide, and triacetin. In addition, the 200 mg tablet coating contains iron oxide red, and the 300 mg tablet coating contains black iron oxide, iron oxide red, and iron oxide yellow. The drug product is supplied in bottles of 14 tablets with an expiry of 30 months when stored at USP controlled room temperature.

There were nine formulations used during clinical development (Module 2.7.1 Summary of Biopharmaceutics Tables 3 and 4); F9 is the intended to-be-marketed formulation. Drug product from F8 and F9 were used in the pivotal clinical trial; comparability of the F8 and F9 300 mg tablets was demonstrated in an in vivo bioequivalence study (Study CC-486-CAGEN-001) and by in vitro dissolution profiles. Based on analytical data and dissolution testing, a biowaiver is granted for the 200 mg tablet.

There were no outstanding safety issues identified for the manufacturing process or from the facilities inspections. The Applicant claimed a categorical exclusion from the requirement for an environmental assessment, and the claim was accepted under 21 CFR 25.31(b). Approval of the NDA was recommended by the Product Quality review team.

4.3 DEVICES AND COMPANION DIAGNOSTIC ISSUES

(b) (4)

The CDRH Reviewer noted that the submission did not include sufficient data to establish the analytical validity of the assay for the level of MRD (b) (4)

5 NONCLINICAL PHARMACOLOGY/TOXICOLOGY

5. 1 EXECUTIVE SUMMARY

Azacitidine, a pyrimidine nucleoside analog of cytidine, incorporates into both deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) and results in anti-leukemic activity in cancers such as AML. The mechanism of the anti-tumor activity of azacitidine involves effects on cell differentiation, cell cytotoxicity, and gene expression; certain effects are attributed to the epigenetic mode of action. Azacitidine exerts anti-AML and MDS activity by inhibiting DNA methyltransferases and causing reduced cytosine methylation in newly synthesized DNA.[1] In AML, aberrant DNA hypermethylation in promoter regions (CpGs) of genes tends to silence gene expression.[2] 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.[1] In addition, azacitidine activates DNA damage and P53 response pathways causing cell death and apoptosis of abnormal hematopoietic cells in the bone marrow. [1,3] Azacitidine incorporates into RNA and decreases ribonucleotide reductase M2 subunit (RRM2) expression and attenuates RRM2 mRNA stability.[4] Azacitidine inhibits RNA:m5C methyltransferases to limit RNA methylation, decreases protein synthesis, and induces cell cytotoxicity.[1,5]

The azacitidine concentrations that affected protein synthesis (2–5 μM) were associated with greater effects on cell viability.[1] Given that the maximal plasma concentrations achieved in patients treated with oral azacitidine (CC-486) were only up to 0.9 μM (Cmax of 0.2-0.9 μM azacitidine),[1,6] the relative impact on protein synthesis remains to be established. However, an azacitidine-induced reduction of AML cell viability (0-20% AML cells survived) was apparent at 1 μM,[1] indicating a potential of azacitidine-associated cytotoxicity at the recommended clinical doses.

Azacitidine, via incorporation into the DNA, blocks cells from entering S-phase in a dose-dependent manner. Thus, the kinetics of azacitidine cytotoxicity depend on the dose of azacitidine; a higher dose of azacitidine results in a longer elapse for repopulation of cells. Diminished antitumor effects may occur when azacitidine is administered in combination with

[1] Hollenbach et al., PLoS One 592): e9001, 2010.
[2] Yoo and Jones, Nature Review Drug Discovery 5(1): 37-50, 2006.
[3] Leung et al., PNAS, 116(2), 695-700, 2019.
[4] Aimiuwu, Blood 119: 5229-5238, 2012.
[5] Cheng et al., Nat Comm 9(1): 1163, 2018.
[6] Laille et al., PLoS One. 10 (8): e0135520, 2015.

cytotoxic agents such as doxorubicin, especially if the cytotoxic agent is administered following azacitidine. In nonclinical studies, an adequate length of time between the administration of the two drugs was needed for maximizing the cytotoxic effect at a high dose of azacitidine in the combination therapy.[7]

Tsai and colleagues indicated that low doses of DNA methylation inhibitors, such as azacitidine, provide antitumor effects over time rather than exerting cytotoxic effects acutely.[8] In vitro, transient exposure of cultured and primary leukemic and epithelial tumor cells to clinically relevant nanomolar doses, produced an antitumor response without causing immediate cytotoxicity, including the inhibition of subpopulations of cancer stem-like cells. These effects were accompanied by sustained decreases in genome-wide promoter DNA methylation, gene re-expression, and antitumor changes in key cellular regulatory pathways.

As most of the toxicology data that supported the approval of Vidaza (azacitidine via the intravenous or subcutaneous routes) under NDA 050794 was crossed referenced, only short-term toxicology studies (≤14 days) of azacitidine administered orally in mice and dogs were reviewed for the current submission. Oral azacitidine exhibited a comparable toxicity profile as azacitidine via injection. Mortality and cytotoxic effects were mainly due to myelosuppression and secondary infections and/or inflammation following lymphoid depletion. The target organs included the bone marrow, lymphoid organs, gastrointestinal (GI) tracts and liver. The toxicities were mostly irreversible during a 3-week recovery period.

Based on the product label for Vidaza (azacitidine for injection), azacitidine is mutagenic, clastogenic, embryotoxic, and teratogenic. In evaluations of fertility, azacitidine caused male reproductive organ toxicity in rats and embryo loss in untreated females mated to treated males. Azacitidine induced tumors of the hematopoietic system, lymphoid tissues, lungs, mammary gland, testes, and skin in rodents.

The labeling for oral azacitidine under this NDA for the AML indication includes updates to the mechanisms of action of azacitidine (Section 12.1). Revisions to other pharmacology/ toxicology-related sections mainly reflect the current FDA labeling practices.

5.2 REFERENCED NDAS, BLAS, DMFS

NDA 050794

[7] Presant et al., JNCI, 67 (60): 1283-1288, 1981.
[8] Tsai et al., Cancer Cell 21: 430-446, 2012.

5.3 PHARMACOLOGY

Recent genomic studies reveal the complexity of the pathobiology of AML which involves the acquisition of cytogenetic, genetic and/or epigenetic alterations in hematopoietic stem or progenitor cells. Such alterations, together with secondary alterations, give rise to leukemic stem cells (LSCs) and an accumulation of AML blasts.[9,10] Azacitidine has multiple mechanisms by which it could be exerting its effects in tumor cells. For an example, azacitidine treatment for MDS has demonstrated dose-dependent effects; at low doses, azacitidine functions as a DNA methyltransferase inhibitor, causing DNA hypomethylation, while at high doses, azacitidine shows direct cytotoxicity to abnormal hematopoietic cells in the bone marrow (BM) through its incorporation into DNA and RNA, resulting in cell death.[11]

5.3.1 Primary Pharmacology

In vitro Pharmacology

Genetic/Epigenetic Alterations and Acute Myeloid leukemia (AML)

Recent studies have shown that cancer is a genetic and epigenetic disease. Next-generation sequencing revealed that more than 50% of human cancers harbor mutations in enzymes that are involved in chromatin organization. Tumor cells not only are activated by genetic and epigenetic alterations, but also routinely use epigenetic processes to ensure their escape from chemotherapy and host immune surveillance.[12] Although DNA methylation together with histone modifications occur in normal hematopoiesis to regulate gene expression and cellular differentiation, aberrant use of these mechanisms is associated with tumorigenesis. Recent large-scale sequencing of AML and MDS genomes revealed that genetic and epigenetic changes co-operate in the pathobiology of myeloid cancers. Aberrant methylation is typically not confined to single genes in AML and occurs across many different genes and chromosomes.[13] AML is characterized by multiple somatically acquired mutations that affect genes of different functional categories and disease development. Mutations in genes encoding epigenetic modifiers, such as DNA methyltransferase 3A (DNMT3A), ASXL1, ten-eleven translocation-2 (TET2), isocitrate dehydrogenase 1 (IDH1), and IDH2, are commonly acquired early and are present in the founding clone. These genes are driving events for epigenetic reprogramming of cells in AML, and their mutations are recurrent. They also contribute to DNA hypermethylation

[9] Shlush et al., Nature 547: 104-108, 2017.
[10] Corces-Zimmerman et al., Proc Natl Acad Sci 111(7): 2548-2553, 2014.
[11] Loiseau et al., Exp Hematol 43:661-672, 2015.
[12] Jones et al. Nat Rev Genet 17:630-641, 2016.
[13] Melki et al., Cancer Res 59: 3730-3740, 1999.

and inhibition of normal cellular differentiation.[14,15] In contrast, mutations involving nucleophosmin (NPM1) genes, which encode multifunctional nucleo-cytoplasmic shuttling protein, or signaling molecules (e.g., FLT3, RAS), typically are secondary events that occur later during leukemogenesis.[16]

In treating four different AML cell lines reflecting a gradient of the differentiation stages along the myeloid lineage with azacitidine, Leung and coworkers described heterogeneous responses to azacitidine. Proteomic data revealed that treatment with azacitidine produced changes in omics, including global reduction of the DNA methylome, upregulation of the transcriptome (five commonly up-regulated coding genes), and upregulation of one gene of the cell-surface proteome. The most prominent responses were the downregulation of metabolism and upregulation of immune defense.[3] The complexity of the acquisition of cytogenic, genetic and epigenetic alterations probably influences the morphological changes of the disease and clinical phenotypes, and determines the prognostic risk of AML.[17]

Mechanism of Action

Cellular update of azacitidine

The cellular uptake of azanucleoside cytidine analogs, such as azacitidine and decitabine, plays an important role in mediating the physiologic-pharmacological effects of these agents. Damaraju et al. investigated the cellular components involved in the uptake and membrane transport of these nucleosides. The research showed that human nucleoside transporters (hNTs) and human concentrative nucleoside transporters (hCNTs) transported azacitidine, with hCNT3 showing the highest rates, whereas human equilibrative nucleoside transporters (i.e., hENT1 and hENT2) showed modest transport.[18, 19] Their data also showed that azacitidine and decitabine exhibit different human nucleoside transportability profiles, and their cytotoxicities are dependent on the presence of hNTs. Tong and coworkers showed that azacitidine uptake was more than 2-fold higher in AML cells than in a normal B-lymphoblast peripheral blood cell line (PBC).[19]

The cellular uptake of azacitidine is mediated by cell membrane nucleoside transporters, and azacitidine is enzymatically phosphorylated by a set of uridine-cytidine kinases and deoxycytidine kinase from a monophosphate derivative to diphosphate and triphosphate forms prior to DNA and RNA incorporation. The metabolic pathway of azacitidine is illustrated in the figure below.[20]

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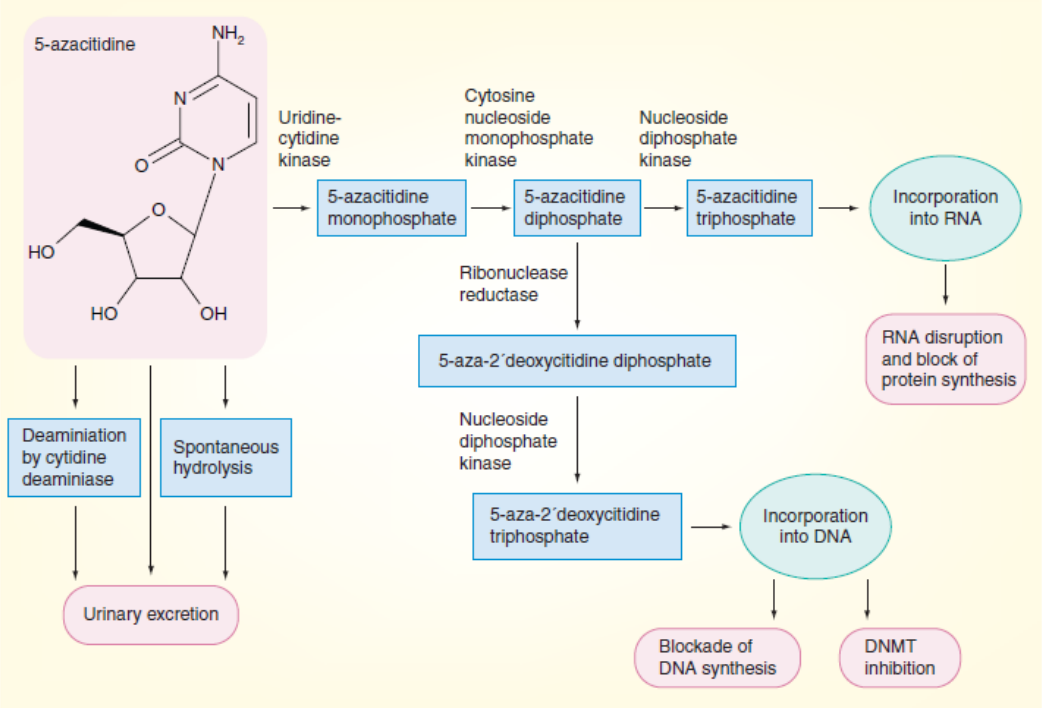
[14] Sun et al., Frontiers in Oncology, 8: 1-16, 2018.
[15] Lio et al., Blood, 134: 1487-1497, 2019.
[16] Bullinger et al., J Clin Oncol 35: 9340946, 2017.
[17] Papaemmanuil et al., N Engl J Med 374: 2209-2221, 2016.
[18] Damaraju et al., nucleosides, Nucleotides and Nucleic Acids, 31: 236-255, 2012.
[19] Tong et al., XENOBIOTICA 49: 1229-1236, 2019.
[20] D'Alo et al., Therapy, 2(5): 717-731, 2005.

Figure 1: Metabolic Pathways of Azacitidine after Cellular Uptake



(Figure from D'Alo, Voso and Leone, 2005) [20]

DNA/RNA incorporation:

As a pyrimidine ring analogue of cytidine, azacitidine is incorporated into RNA as a false substrate (5-aza-CTP), causes alterations in RNA synthesis and processing, and results in the inhibition of protein synthesis. Azacitidine can be converted as the deoxynucleotide (5-aza-dCTP) and is then incorporated into DNA, inhibiting its synthesis and blocking cytosine methylation by noncompetitive inhibition of DNA methyltransferase. The resulting hypomethylation of DNA induces gene activation and expression as well as cell differentiation. Using murine L1210 leukemia cells as a model system, azacitidine was incorporated into RNA to a higher extent than into DNA (80 to 90% versus 10 to 20% of total incorporated).[21] According to different reports, RNA incorporation accounts for approximately 65% to 90% of the azacitidine incorporated into cellular nucleic acid.[1,4]

DNA methylation and tumorigenesis

DNA methylation

DNA methylation is conventionally referred to as a modification to the 5-position of a cytosine

[21] Li et al., Cancer Res. 30 (Nov): 2760-2769, 1970.

ring (i.e., 5-methylcytosine) that occurs most commonly in the context of a CpG palindrome in DNA that can be transmitted to daughter cells at cell division and has been implicated in the regulation of gene expression. In mammals, DNA is methylated mainly by any of three DNA methyltransferases (DNMT1, DNMT3a, and DNMT3b).[22] It is now generally accepted that the presence of 5-methylcytosine in DNA has epigenetic effects on gene expression (including expression of micro-RNAs) and cellular differentiation.[12] The DNA hypomethylation effect of azacitidine may be attributable to the inhibition of the formation of 5-methylcytosine through the inhibition of methyltransferases. The inhibitory actions of azacitidine on DNA methyltransferases (DNMTs), aberrant methylation at promotor CpG islands and the microRNAs regulating DNMTs are discussed below.

DNA methylation on CpG island

DNA cytosine methylation in vertebrates is virtually restricted to cytosine nucleotides in the sequence CG (CpG; cytosine-guanine).[23] In the mammalian genome, CpG dinucleotides account for less than 20% of their expected frequency based on the CG content, owing to the progressive mutation of 5-methylcytosine to thymine through deamination during evolution. CpG dinucleotides may cluster as a CpG island (CGI), which serves as a functional unit to regulate gene expression through binding to transcription factors.[24] A CGI is defined as clusters of CpG dinucleotides with a high CG content of over 50% and an observed/expected CpG ratio larger than 0.60 in any genomic region of at least 200 bp. Of note, CGIs are associated with over 50% of human gene promoters and are involved in regulating gene expression.[25] Imbalance of gene expression due to the aberrant DNA methylation of gene promoters has been implicated in human diseases, including cancer.

Although focal hypermethylation at gene promotors or CpG islands may interfere with the binding of transcription factors, it appears that the major mechanism of gene silencing results from the binding of repressor proteins to methylated DNA.[24] More updated evidence suggests that promoters can be divided into those with and without CGIs, and promoters have different marks relative to those on enhancers or gene bodies.[26] Most of CGI are not methylated when located at transcription start sites, and gene body methylation contributing to cancer would cause somatic and germline mutations.[26]

Hypermethylation in gene promoter regions is one of the most widespread epigenetic changes

[22] Edwards et al., Epigenetics & Chromatin 10: 23-32, 2017.
[23] Cooper Hum Genet 64: 315-333, 1983.
[24] Nan et al., Novartis Found Symp. 214: 6-16, 1998.
[25] Takai and Jones, PNAS 99 (6): 3740-3745, 2002.
[26] Jones Nat Rev Gene 13 (7): 484-492, 2012.

found in multiple cancers, and it is often linked with genomic instability.[27] Cancer cells are characterized by the gene-specific hypermethylation of promoter CpG islands, leading to the downregulation or loss of gene expression.[27] These hypermethylated genes are involved in numerous cellular pathways reflecting hallmarks of cancer, such as cell cycle regulation, DNA repair, hormone response, cell adhesion, signal transduction and apoptosis.[27] Regulation of various genes in the KG-1a AML cells by azacitidine may partly be due to the suppression of the hypermethylation in gene promotor regions.[1] The cause of aberrant hypermethylation of CpG islands is unclear, but de novo methylation has been shown to increase with age.[28] Over-expression of DNA methyltransferases may also contribute to hypermethylation of CpG islands.[27]

MicroRNAs: methylation and epigenetics

MicroRNAs (miRs) are short noncoding RNAs that modulate gene expression by negatively regulating stability or translational efficiency of the target mRNA.[29] In addition to the roles in the maintenance and regulation of biophysiological functions, deregulation of miRs has been shown to contribute to the development of a variety of tumors, such as leukemia.[30] Aberrant expression of miRs was shown to have crucial roles in tumor progression and the development of chemoresistance. For these reasons, miRNA expression analyses have been applied to tumor diagnosis, treatment, and prognostic prediction.

- Tumor suppressive role of microRNAs

There is evidence that dysregulation of microRNAs occurs in a subset of AML and involves methylation-based silencing of tumor suppressors leading to oncogenesis. In MDS and AML, the DLK1–DIO3 region contains a large miRNA cluster, and overexpression of these miRNAs is associated with aberrant hypermethylation of the locus.[31,32] Merkerova et al. reported that the expression levels of miRNAs were reduced in CD34+ bone marrow cells from the patients with high-risk MDS and AML after the treatment of asacitidine.[31] Several miRs have been described in the literature for their roles in MDS and AML. MiR-21, a representative oncogenic miRNA, has prognostic significance in many cancers and can modulate the sensitivity to chemotherapeutic agents. Kim and colleagues reported that the serum miR-21 level was significantly associated with the prognostic outcomes in MDS patients treated with hypomethylating agents, such as azacitidine.[32] The baseline level of serum miR-21 was significantly lower in the responder group

[27] Schubeler Nature 517 (7534): 321-326, 2015.
[28] Kwabi-Addo et al., Clin Cancer Res 13 (13): 3796-3802, 2007.
[29] Lin, Curr Opin Cell Biol 20: 214-212, 2008.
[30] Calin et al., PNAS 01: 11755-11760, 2004.
[31] Merkerova et al., Cells, 7 (9): e138-, 2018.
[32] Kim et al., PLoS One, 9 (2): e86933, 2014.

than in the non-responder group. In addition, miR-370 functions as a tumor suppressor by targeting FoxM1 and the silencing of miR-370 could lead to de-repression of FoxM1 expression and consequently AML progression.[33] Epigenetic inactivation of miR-9 has been described in pediatric AML with EVI1 expression and the underlying mechanism was attributable to methylation of the miR-9 promoter.[34]

- Deregulation of miRNA expression by DNA methylation

The potential role of miRNA methylation as a biomarker for diagnosis, prognosis (and hence the potential of developing a risk-stratified approach) and a therapeutic target have been investigated. Solly and coworkers described a miRNA-DNMT1 axis and its involvement in azacitidine resistance.[35] In patients treated with azacitidine, decreased expression of anti-DNMT1 miRNAs was associated with poor outcome. Ectopic anti-DNMT1 miRNA expression decreased DNMT1 expression and increased azacitidine sensitivity, whereas specific inhibition of endogenous anti-DNMT1 miRNAs increased DNMT1 expression and triggered azacitidine resistance. DNMT1 is targeted by miR-126 which interacts with the 3'-untranslated region (UTR) and inhibits DNMT1 translation without altering its transcription.[36] Thus, decreased miR-126 expression negatively influenced the response to azacitidine and independently predicted poor treatment outcomes. In the investigation of the miR-34 family, Wong's group described deregulation of miRNA expression by DNA methylation found in epithelial and hematological cancers.[37] The aberrant DNA methylation of gene promoters has been shown to result in the inactivation of tumor suppressor genes, and therefore is also implicated in carcinogenesis. In summary, evidence indicates that the anti-tumor activity of azacitidine is associated with the inhibition of the miRNA-DNA methyltransferase axis. The anti-DNA methylation effect of azacitidine may restore the deregulation of miRNA expression, and lead to suppression of tumorigenesis.

DNA hypomethylation effect of azacitidine (Inhibition of DNA methylation)

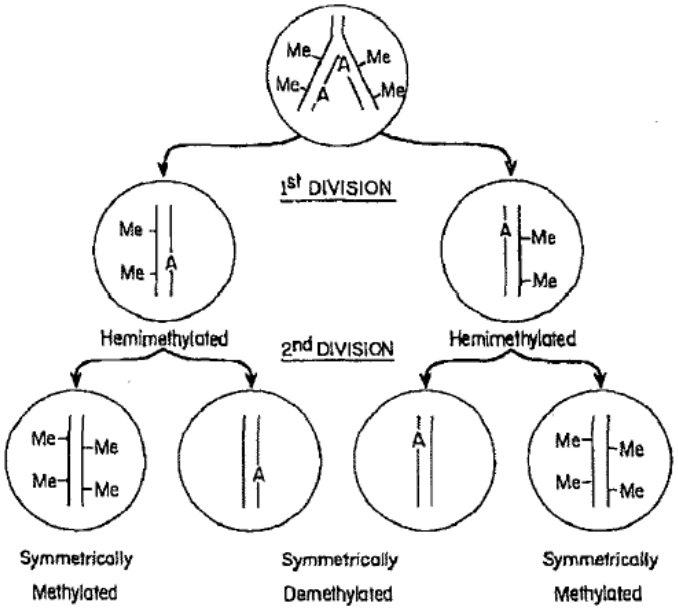
<u>Azacitidine inhibits DNA methyltransferases</u>

Azacitidine inhibits the methylation of newly synthesized DNA strands by inhibiting DNA methyltransferase activity; the pivotal anti-tumor activity of azacitidine is inhibition of DNA methyltransferases (DNMT1, DNMT3a, and DNMT3b).[22] Since azacitidine incorporated into DNA cannot be methylated, azacitidine serves as a false substrate. By incorporating into DNA, azacitidine facilitates the formation of a tight-binding DNMT-DNA complex and the DNMTs

[33] Zhang et al., Mol Cancer 11:56-66, 2012.
[34] Mittal et al., Mol Cancer 18 (1): 30-35, 2019.
[35] Solly et al., Clin Cancer Res. 23 (12): 3025-3034, 2017.
[36] Zhao et al., Arthritis Rheum 63: 1376-1386, 2011.
[37] Wong, et al., Epigenomics 3(1): 83-92, 2011.

become trapped on the substituted DNA strand. Thus, DNMTs are inactivated, and methylation of the new DNA strand is prevented. The resultant azacitidine-DNA methyltransferase irreversible complex leads to the depletion of available enzymes (See the figure below, Jones 1983).[38]

Figure 2: Inhibition of DNA Methyltransferases by Azacitidine (Hypomethylation)



The replication of DNA containing 5-methylcytosine (Me) in the S phase is shown at the top of the diagram. If 5-azacytosine (A) was incorporated into the newly synthesized DNA and inhibited DNA methylation, the daughter cells of the first division would contain hemimethylated DNA in the sequence controlling gene expression. Symmetrically demethylated DNA in this sequence would result after the second division following treatment, because of the specificity of the DNA methyltransferase.
(Figure from Jones et al, 1983)[38]

Research data indicated that azacitidine's effect on DNA hypomethylation is dose-dependent, with epigenetic mechanisms favored at lower concentrations and cytotoxic mechanisms occurring at higher concentrations.[39] Investigations also supported the notion, that DNA methylation inhibitors, such as azacitidine, activate the DNA damage response pathways and result in cytotoxicity. Although, the exact relationship between the azacitidine-induced hypomethylation and cytotoxicity has not been determined, cumulative evidence suggests that DNA methyltransferase/DNA adduct formation in cells treated with azacitidine analogs may activate the p53 pathway (indicated as expression of p21), culminating in cell death by apoptosis.[40] Previously, studies by Kuo et al. demonstrated that azacitidine-induced DNA methyltransferase-DNA adducts block the progress of DNA replication in vivo in *E. coli*. [41]

[38] Jones et al., Recent Results Cancer Res 84: 202-211, 1983.
[39] Jones and Taylor, Nucleic Acids Res 9 (12): 2933-2947, 1981.
[40] Jiemjit et al., Oncogene 27 (25): 3615-3623, 2008.
[41] Kuo et al., Cancer Res 67 (17): 8248-8254, 2007.

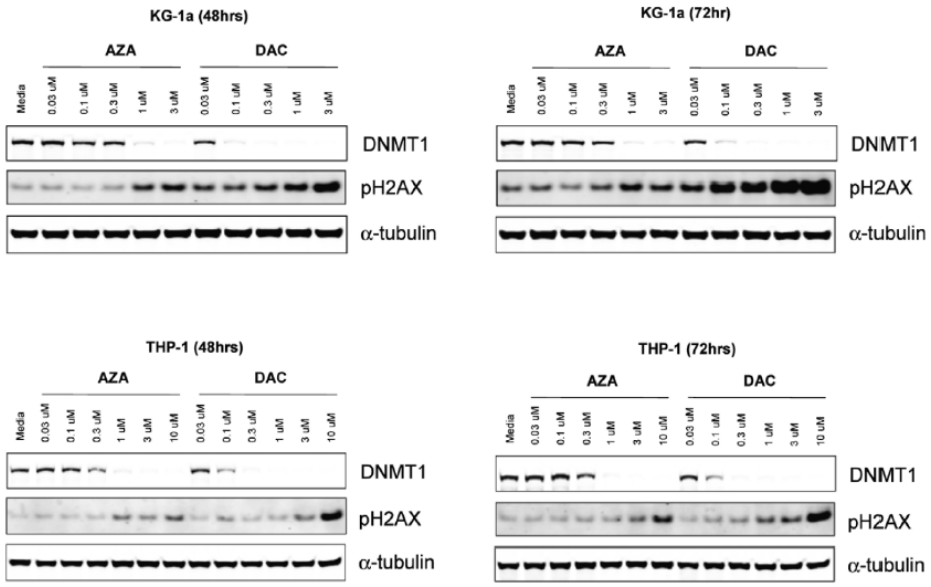
Azacitidine may impact regulation of numerous genes previously silenced by hypermethylation. Re-expression by the hypomethylating effect of azacitidine results in modification of multiple cellular pathways. This action is shared by another DNA methylation inhibitor, decitabine. However, despite the shared mechanisms of action of azacitidine and decitabine on DNA-mediated markers of activity, incorporation of azacitidine into both DNA and RNA induced distinctly different cellular effects on cell viability, protein synthesis, cell cycle, and gene expression.[1]

DNA-mediated effects of azacitidine in AML cell lines

The following is mainly the summary of Hollenbach and coworkers' research in the AML cell lines KG-1a and THP-1. Decitabine (5-aza-2'-deoxycytidine) will become 5-aza-2'-dCTP and incorporate into DNA like azacitidine. In a comparison of the two DNA methylation inhibitors (hypomethylation agents) azacitidine (AZA) and decitabine (DAC), the authors summarized the commonly shared effects and the differences between these two agents.[1]

Effects in common: Both agents reduced DNA methylation (inhibition of DNMT1), induced DNA damage (as measured by phosphorylation of the histone H2A variant, H2AX, at serine 139 to generate γ-H2AX) in KG-1a and THP-1 cells as shown in the figure below, and increased markers of apoptosis in KG-1a cells. The subsequent impact of DNMT1 inhibition by AZA and DAC corresponded with decreases in global DNA methylation in KG-1a and THP-1 cells (data not shown).

Figure 3: AZA and DAC Cause Depletion of DNMT1 Protein and DNA Damage in KG-1a and THP-1 Cells

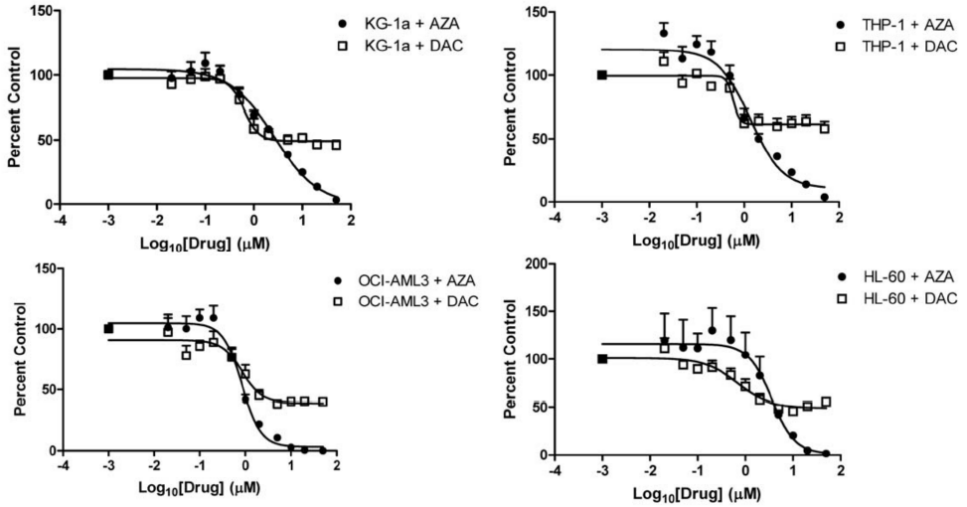


AML cell lines were treated daily with azacitidine (AZA) or 5-aza-2'-deoxycytidine (DAC) (0–3 mM in KG-1a; 0–10 mM in THP-1) for 48 and 72 hours. Protein lysates were analyzed by Western analysis for DNMT1 and phospho-H2AX (Ser 139) proteins. a-Tubulin is shown as a protein loading control. DNMT = DNA methyltransferase.
(Figure from Hollenbach et al, 2010)[1]

Using a LINE-1 DNA methylation assay (DNA elements in bisulfite-converted DNA), both AZA and DAC demonstrated DNA hypomethylation effects (data not shown).

Different effects: Azacitidine exhibited a more potent reduction in cell viability at ≥ 5 μM (0-20% cell viability observed), while decitabine did not reduce cell viability below 40% at any concentration up to 50 μM. The difference between the two agents was also illustrated in the concentration-response curves shown below.

Figure 4: Azacitidine and Decitabine (DAZ) on Cell Viability



(Figure from Hollenbach et al, 2010)[1]

Azacitidine and decitabine also have different effects on protein synthesis. Metabolic labeling (^{35}S-methionine and ^{35}S-cysteine) of KG-1a and THP-1 cells after 24 and 48 hours of daily drug treatment showed that 2 μM azacitidine reduced protein synthesis by 41% and 43% at 24 hours, and 51% and 58% at 48 hours, respectively. The inhibition of protein synthesis was not observed with decitabine, which incorporates predominantly into DNA. AZA may have activity in cells during all phases of the cell cycle via RNA incorporation, whereas DAC incorporation into DNA is restricted to the S-phase.

As described in the table below, azacitidine (1 μM) most significantly regulated biogroups representing metabolic processes, aminoacyl-tRNA ligase activity, and mitochondrion at 24 hours, as well as mitosis, cell cycling, and cell division at 48 hours. In contrast, decitabine (1 μM) significantly upregulated the cell differentiation biogroup at 24 and 48 hours. Thus, shared mechanisms of action of AZA and DAC on DNA-mediated markers of activity were demonstrated, but distinctly different effects in their actions on cell viability, protein synthesis, cell cycle, and gene expression were also observed. The differential effects of AZA may be mediated by RNA incorporation, which predominates intracellularly; the distribution of AZA in nucleic acid of KG-1a cells was 65:35, RNA:DNA.

Table 1: Gene Biogroups regulated by AZA and DAC in KG-1a Cells

GO category	1 μM AZA, 24 hours *P*-value (direction)	1 μM DAC, 24 hours *P*-value (direction)
Sterol metabolic process	1.0E-15 (down)	
Ligase activity, forming aminoacyl-tRNA and related compounds	3.8E-12 (up)	
Lipid metabolic process	4.1E-11 (down)	
Mitochondrion	3.3E-10 (down)	0.0023 (down)
Cell differentiation	0.0014 (up)	2.1E-9 (up)
Co-factor binding	1.9E-8 (up)	4.3E-7 (down)
GO category	**1 μM AZA, 48 hours *P*-value (direction)**	**1 μM DAC, 48 hours *P*-value (direction)**
Mitosis	3.0E-53 (down)	
Cell cycle	9.1E-46 (down)	0.0088 (down)
Cell division	4.9E-44 (down)	
Chromosome	2.6E-26 (down)	
Response to DNA damage stimulus	8.2E-22 (down)	0.0002 (down)
Ligase activity, forming aminoacyl-tRNA and related compounds		2.4E-17 (down)
Cytoskeleton	2.3E-12 (down)	0.0006 (up)
Cell differentiation	0.0024 (up)	4.4E-12 (up)

Biogroups of genes regulated ≥1.7-fold by daily treatment with AZA (1 μM) or DAC (1 μM) in KG-1a cells at 24 and 48 hours. Directionality indicates the predominant direction of gene regulation within each biogroup. P-values of low significance are included for biogroups regulated by both drugs, but highly significant for only one drug. AZA = azacitidine; DAC = decitabine.

(Table from Hollenbach et al, 2010)[1]

DNA methylation inhibitors in immune-oncology

DNA methylation inhibitors, such as azacitidine, can not only reactivate genes, including tumor suppressors that have acquired DNA methylation during carcinogenesis, they can also induce the expression of thousands of transposable elements such as endogenous retroviruses (ERVs) and latent cancer testis antigens (CTAs) normally silenced by DNA methylation in most somatic

cells. Furthermore, these changes mediated by DNA methylation inhibitors can also alter the function of immune cells relevant to acquired immunity.[42]

Immunoregulation

The regulatory T cells (Tregs) are important for homeostasis of the immune system. Immune regulation by Tregs depends on the stability of these cells, which in turn is controlled by stable expression of the transcription factor forkhead box P3 (FOXP3).[43,44] Optimal FOXP3 expression strongly depends on hypomethylation of the FOXP3 gene. Thus, DNA methyltransferase inhibitors theoretically would promote Treg stability. In an in vitro study of the activation of Treg, the supplement of DNA methyltransferase inhibitors, such as azacitidine, led to a significant inhibition of Treg proliferation and promotion of T helper-1 (Th1) polarization; however, Tregs maintained their suppressive capacity. Treatment with DNA hypomethylation agents did not induce an inhibition of naïve conventional CD4+ T cells (Tconv).[44]

Immune modulatory effects in bone marrow microenvironment

Azacitidine also exerts antineoplastic effects by epigenetic regulation of the bone marrow microenvironment, including specific immune-mediated pathways associated with innate and adaptive immunity. Treating AML cell lines with azacitidine, Leung et al. found the most prominent responses were the down-regulation of metabolism and up-regulation of immune defense.[3]

Effects on RNA hypomethylation

RNA hypomethylation

Aimiuwu et al reported that azacitidine downregulated ribonucleotide reductase-M2 subunit (RRM2) expression through RNA incorporation and attenuates RRM2 mRNA stability.[45] Through RRM2 inhibition, azacitidine induced a reduced deoxyribonucleotide pool and impacted DNA synthesis and repair. Research data indicated that incorporation of azacitidine into tRNA, rRNA, and mRNA resulted in alterations in RNA synthesis and processing and concomitant inhibition of protein synthesis. Investigation of the effects following azacitidine incorporation into RNA by Cortvrindt and coworkers demonstrated that the addition of an excess cytidine inhibited the antiproliferative or cytotoxic activity of azacitidine. The excess cytidine served as a competitive nucleoside for RNA/DNA suppression by azacitidine. The authors concluded that the inhibition was mainly due to inhibition of the phosphorylation of

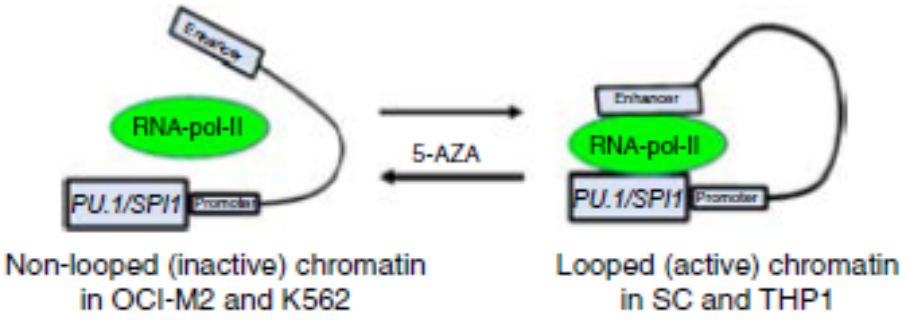
[42] Jones et al., Nat Rev Cancer 19: 151-161, 2019.
[43] Sakaguchi et al., Nat Rev Immunology 10 (7): 490-500, 2010.
[44] Landman et al., J Immunology Research, 2018:4973964, 2018.
[45] Aimiuwu et al., Blood 119 (22): 5229-5238, 2012.

azacitidine and not competition for intracellular transport. In contrast, the addition of an excess of deoxycytidine serving as a competitor for incorporation with azacitidine into DNA only, was either without effect or potentiated the antiproliferative effect of azacitidine.[46] With regard to the dose-dependence of the effects of azacitidine on DNA hypomethylation, Murakami et al. reported that the cytotoxic effects of low dose azacitidine on cells in G1 may be mediated mainly through RNA and that cytotoxicity at higher dose levels in cells in G1 and S phases is mediated through incorporation into both RNA and DNA.[47]

RNA 5-methylcytosine (RNA:m^{5}C) and RNA:m^{5}C methyltransferases (RCMTs)

The RCMTs, namely NSUN3 and DNMT2, directly bind hnRNPK, a conserved RNA-binding protein. hnRNPK interacts with the lineage-determining transcription factors (TFs) GATA1 and SPI1/PU.1, and with CDK9/P-TEFb to recruit RNA-polymerase-II at nascent RNA, leading to the formation of the 5-azacitidine (5-AZA)-sensitive chromatin structure.[48] In contrast, NSUN1 binds BRD4 and RNA-polymerase-II to form an active chromatin structure that is insensitive to 5-AZA. Azacitidine inhibited NSUN3 and DNMT2 to limit RNA methylation. These researchers proposed a novel RNA:m^{5}C/RCMT-mediated chromatin structure that would modulate azacitidine response (e.g., ASLCs line) or resistance (e.g., ARLCs line) in azacitidine-treated leukemia cells. A significant increase in RNA:m^{5}C and NSUN1-/BRD4-associated active chromatin is observed in clinical 5-AZA-resistant MDS/AML specimens, supporting the potential clinical relevance of this working model.

Figure 5: Lineage-Associated Drug-Responsive (Active) or Resistance (Inactive) chromatin structural Changes in Leukemia Cells



A schematic summary of these data suggesting opposite transformations of the chromatin conformation at SPI1/PU.1 in erythroid vs. monocytic leukaemia cells in response to 5-AZA.
(Adapted from Cheng et all, 2018)[50]

[46] Cortvrindt et al., Br. J. Cancer 56: 261-265, 1987.
[47] Murakami et al., Cancer Res 55 (14): 3093-3098, 1995.
[48] Cheng et al., Nature Communications, 9: 1163-1178, 2018.

In vivo Pharmacology

Study # Azacitidine-DMPK-2808 that investigated the biodistribution of azacitidine into DNA/RNA of blood and bone marrow is summarized in the ADME/PK section of this review.

A series of studies in leukemia AML models were employed to assess the mechanistic and therapeutic activity of lower-exposure, extended-dosing regimens of azacitidine. These models included a C1498-Luc-GFP syngeneic AML model in B6 albino mice, a FLT-ITD Tet2 mouse genetic AML model, a mouse Cdx2 genetic AML model, and human AML models, including Molm-13 and two patient derived AML xenografts. These in vivo studies (the respective study number as indicated) were reviewed, and the results are summarized in the table below. In conclusion, azacitidine demonstrated significant in vivo activity, indicating the potential for therapeutic utility in AML. Activity was observed using either exposure-schedules of high exposure-limited duration (HELD) or low exposure-extended duration (LEED).

Summary of Study Reports in Models of Leukemia

Model	Description	Dose, schedules	Results
Mouse syngeneic cell line model (C1498-Luc3-GFP) Report SF-2018-CC486-BZ-001	Syngeneic Acute Myeloid Leukemia C1498-Luc3-GFP Model in B6 Albino Mice	Azacitidine intraperitoneal (IP) as HELD, 5 mg/kg QDx4; or LEED, 1 mg/kg QDx20	Both dosing regimens were generally tolerated (no body weight reduction). Significant changes with both regimens included: ↓tumor burden and prolonged survivals, ↓C1498 GFP expressing tumor cells in the peripheral blood (PB), bone marrow (BM) and spleen, and ↓total and differential white blood cell counts. At LEED: ↓% myeloid derived suppressor cells (MDSCs) in the blood, BM and spleen, ↓ erythroid parameters, and ↑% CD4+ and CD8+ T cells in the blood, BM and spleen. HELD ↑ % CD4+ cells only in the BM.
Mouse AML model: FLT3-ITD and TET2 loss Report SF-2019-CC486-DM-001	Chimeric AML model, BM from FLT3-ITD; TET2; lysozyme M-cre recombinase (LysM-cre) compound heterozygous mice (FLT3-+/TET2-+/LysM-cre-/+) on a cluster of differen-tiation 45.2 (CD45.2) C58BL6 background was transferred via (IV) into irradiated 8-week-old congenic CD45.1 C57BL6 wild type (WT) recipient mice	IP azacitidine as LEED (1 mg/kg for 5 days, 2 days off, for 3 weeks); HELD (3 mg/kg for 5 days)	Both LEED and HELD: resolving splenomegaly (an indicator of AML disease progression) and ↓% undifferentiated blasts in the blood and spleen (LEED also ↓ blasts in BM) In comparison to HELD, LEED resulted in the following: 1) more sustained, continuous suppression of blood cell counts, 2) the closest resolution of AML tissue pathology, 3) more sustained continuous activity of suppression of myeloid lineage cells and/or reduction of myeloid lineage populations in the blood, BM and spleen, 4) more effective at ↑ % CD3+ T cells in the blood, 5) only LEED induced significant ↑% CD3+ T cells in the spleen and % CD8+ T cells in the BM and spleen. In conclusion, LEED dosing enhances immune cell function by increasing the percentage of cytotoxic T cell populations.
Mouse Cdx2 AML genetic model Report SF-2019-CC486-DM-002	Inducible transgenic mouse model in which Cdx2 was specifically activated in HSCs; C57BL/6 Scl-CreERT, and LSL-Cdx2-	IP azacitidine as LEED (1 mg/kg for 5 days, 2 days off, for 3 weeks, CC-486 like); or 1 mg/kg for 2 weeks	LEED in comparison to HELD: ↑overall survival and sustained reduction in PB WBC counts, suggesting that dose and scheduling may be relevant in optimizing clinical responses to azacitidine in MDS/AML. In the gene set enrichment analysis: results demonstrated treatment-associated hypomethylation in

Model	Description	Dose, schedules	Results
	Cherry; tamoxifen (400 mg/kg feed)	HELD (2 mg/kg for 7 days, 3 weeks off, Vidaza like)	the gene set signature for DNA damage and apoptosis
Human AML MOLM-13 xenograft model* Report SF-2019-CC486-DD-002	MOLM-13 AML cell line containing a FLT3 internal tandem duplication (ITD) mutation intravenously injected into female NOD/SCID mice	IP azacitidine as LEED (1 mg/kg for 5 days, 2 days off, for 3 weeks); HELD (3 mg/kg for 5 days); in combination with gilteritinib, midostaurin or venetoclax	Both regimens elicited statistically significant increases in survival. Combination with either midostaurin, gilteritinib or venetoclax led to statistically significant increases in survival vs azacitidine alone.
AML human FLT3-ITD patient derived xenograft model (AML-PDX1) Report SF-2019-CC486-DD-003	Human FLT3-ITD AML PDX1 xenograft model injected into the tail vein of NSG mice	IP azacitidine as LEED (1 mg/kg/day for 15 days); HELD (3 mg/kg/day for 5 days)	Both regimens prolonged survival of AML-PDX-1 engrafted mice and ↓blast cells bearing leukemic stem cell markers CD33, CD34 or CD38. HELD significantly ↓ the fraction of human CD45+ cells in the spleen.
AML patient derived xenograft model (CTG-2227) Report SF-2018-CC486-BZ-002	Human AML cells (CTG-2227) were injected into the tail vein of sub-lethally irradiated, immuno-compromised mice (NOG-EXL)	IP azacitidine as LEED (1 mg/kg/day for 25 days); HELD (5 mg/kg/day for 5 days)	LEED dosing decreased body weight by 9% by the end of the study and ↓erythroid parameters, while HELD was tolerated. Both regimens ↓ WBC and neutrophil levels and significantly ↓spleen weight. Based on immunopheno-typing, both regimens ↓ hCD45+ cells in the blood, BM and spleen and ↓CD33+CD117+ and CD33+CD123+ cells in the BM and spleen. LEED ↓CD3-CD33+ myeloid cells in the spleen. No significant changes in variant allele frequency (VAF) were observed in six AML mutations identified in five genes (DNMT3A, IDH1, GATA2, NPM1, and CUX1) by next-generation sequencing (NGS).

5.3.2 Secondary Pharmacology

Myelosuppression

Using in vivo animal models, several researchers documented the immunosuppressive effects, which may be attributed to the nucleic acid incorporation of azacitidine. Vadlanmudi and coworkers conducted experiments in nonleukemic mice to determine the effects of the treatment with azacitidine and uridine on the bone marrow cells and the colony forming ability (as colony forming unit, CFU) of these cells.[49] Co-treatment with uridine reduced the toxic effect of azacitidine on bone marrow cells (reduced survival in comparison to the control) and alleviated the reduced CFU value.

Immunosuppression

Experiments also evaluated the simultaneous treatment of azacitidine and uridine on hemagglutinin synthesis and the hemolytic plaque-forming ability of the spleen cells. To evaluate the effect of azacitidine on antibody formation, nonleukemic mice were injected with

[49] Vadlamudi et al., Exp Biol Med 133(4): 1232-1238, 1970.

sheep red erythrocytes (SRBC) before or after drug treatment. Sera from the treated mice were tested for hemagglutination (HA) titer. Azacitidine treatment suppressed the hemagglutinin synthesis, and uridine reversed the suppression. Similarly, in the spleen colony assay, azacitidine reduced hemolytic plaque-forming cells (PFC) per spleen of mice, and co-treatment of uridine increased PFC.

In Paluska et al., the immunosuppressive effects of azacitidine on skin grafts were illustrated in graft versus host (GVHD) rodent models.[50] Intraperitoneally administered azacitidine prolonged the life span of skin grafts. Two-hour incubation of cells with azacitidine in vitro significantly reduced the GVHD reactivity and capacity to form hemopoietic spleen colonies.

The hypomethylation of DNA by azacitidine has been correlated with the depression of genes, including genes involved in organ development and differentiation. Young Sprague-Dawley rats (males, 3-4 weeks) were treated with azacitidine.[51] Azacitidine caused a pronounced reduction in thymus and spleen weight, but lymphocytes from these organs maintained a normal response to the T-cell mitogen concanavalin A. The reduction in lymphoid tissue weight was attributed to altered gene expression rather than the inhibition of DNA replication, since an inhibitor of DNA replication (cytosine-arabinoside) did not affect the rapid thymus involution triggered by azacitidine.

Antimicrobial and antiviral activity

In the literature, the antibiotic property of azacitidine was demonstrated in some gram-negative bacteria. The inhibition by 5-azacytidine of *E. coli* ATCC 26 was reversed by several pyrimidines, such as cytidine and uridine.[52] The result supported that the antimicrobial effect was mediated through incorporation into RNA and DNA. Although azacitidine inhibited T-4 lymphoma and L-1210 leukemia in mice, azacitidine was ineffective against E. coli infection in mice.[9] The antiviral activity of azacitidine (20-50 μg/mL) was also seen in several virus strains, such as RNA phage f2 and T4 coliphage.[53]

Viral gene expression

Addition of azacitidine in virus culture medium enhanced the expression of endogenous and exogenous viral genes, indicating the possible role of methylation in latency of virus genome.[54] The viral reactivation was characterized by increased viral replication and increased viral antigen expression in the cell cultures. On the other hand, many viral proteins possibly have direct interaction with epigenetic regulators, such as DNA methyltransferases or histone deacetylases.[55]

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[50] Paluska et al., Immunology 162(3): 288-296, 1982.
[51] Csordas and Schauenstein, Bioscience Reports, 6(7): 603-612, 1986.
[52] Hanka et al., Antimicrob Agents Chemother, 6:619-624, 1966.
[53] Rada and Doskocil, Pharmax Ther, 9: 171-217, 1980.
[54] Fynan et al., J Gen Viral 74(Pt 10): 2163-2170, 1993.
[55] Flanagan, Br J Cancer, 96(2): 183-188, 2007.

5.3.3 Safety Pharmacology

In vitro studies

Type of study	Test system	Study design; Salient findings
Cardiac function (#B081078)	Isolated guinea pig hearts: perfused Langendorff model	10, 20 and *40 µmol/L (µM); vehicle: 1% D-mannitol sodium No consistent effect was found on the left ventricular pressure or its dP/dt_{max} (index of cardiac contractility). No effects on the heart rate or perfusion flow (index of the coronary blood flow) were observed.
Chronotropic effects (#B081079)	Isolated guinea pig right atria	10 and **20 µmol/L (µM); vehicle: 1% D-mannitol sodium (1000-fold diluted), positive control: isoproterenol The spontaneous beating rate of the right atria was measured for 30 minutes after treatments. Isoproterenol at 0.1 µM remarkably increased the spontaneous beating rate continuously from 1 to 30 minutes after treatment. Azacitidine did not increase the spontaneous beating rate at 10 and 20 µM, but slightly decreased at 40 µM. The result indicated that although azacitidine had no positive chronotropic effect on the pacemaker activity, it had a weak negative chronotropic effect. The tachycardia seen in the dog may be secondary to hypotension in the dog.
Vasodilatory effects (#B081462)	Isolated rat aorta ring preparations	10, 20 and *40 µmol/L (µM); vehicle: 1% D-mannitol sodium No changes in vasodilatory parameters were observed.

*Greater that the Cmax level (7290 ng/mL, approximately 30 µmol/L) achieved in the conscious dog telemetry study; also, at ≥ 4 mg/kg azacitidine induced significant hypotension, suggesting possible effects on vasodilatory parameters.
**In the dog telemetry study, marked tachycardia at ≥2 mg/kg, was observed suggesting that azacitidine may have had a positive chronotropic effect. However, since doses of 4 mg/kg or more in the dog telemetry study caused significant hypotension, the possibility that the tachycardia was a response to the hypotension could not be excluded.

In vivo studies

No in vivo safety pharmacology studies for the assessment of vital organs were conducted with oral azacitidine (CC-486). Several non-GLP single-dose studies with intravenous administration were conducted to characterize the central nervous system (CNS; Report B071376), respiratory (Report B090393), and cardiovascular (CV; Report B071377) effects of azacitidine.

Type of study	Test system	Study design; Salient findings
Effects on the CNS (#B071376) Irwin's test	Male SD rats Single IV (over a period of 10 min) doses at 10, 20, 30 and 40 mg/kg	Observations were performed at 8 hours, and I, 2 and 7 days after drug administration. Clinical signs: Fecal changes: soft stool at ≥10 mg/kg and diarrhea at ≥ 20 mg/kg Other changes: ↓spontaneous locomotor activity, muscle tone and reactivity to stimuli with palpebral closure and lowered body temperature at ≥30 mg/kg These signs were seen at 10 and 20 mg/kg at 4hr-1 day) and at 30 and 40 mg/kg at 8 hr-7 days after dosing. The suppressive effects on activity at ≥20 mg/kg were secondary to the cytotoxic effects of azacitidine (such as GI signs) instead of direct CNS suppression. TK data (see below)
Effects on the cardiovascular system (#B071377)	Male beagle dogs Single IV (over a period of 10 min) doses following the order of 4, 2 and 6 mg/kg with a 7- to 13-day interval between each administration (2 mL/kg); vehicle: 1% D-mannitol sodium (2 mL/kg)	Parameters: clinical signs/mortality, blood pressures (BP; systolic, diastolic and mean), ECG (duration and waveform), clinical pathology and necropsy. Hemodynamic and ECG parameters: ↓BP, ↑heart rate; ECG: ↓PR and ↑QTc interval (see table below). The ECG findings, especially QTc prolongation was due to lowered plasma K+ levels (<3.3 mmol/L) and Na+ levels. The lower serum Na+ and K+ levels were likely due to vomiting and diarrhea. Mortality: one of five dogs died 7 days after administration at 4 mg/kg, Necropsy: lesions in hemopoietic and lymphoid tissues, hemorrhage and inflammation in multiple tissues, and opportunistic infections due to suppression of white blood cell counts. Azacitidine induced expected cytotoxic effects, including decreased body weights and food consumption, GI-related clinical signs (vomiting, fecal changes), skin lesions, ↓spontaneous locomotor activity, bone marrow toxicities (myelosuppression in all three lineages), and changes in clinical chemistry parameters (increased liver enzymes, creatine kinase (CK), CK isozyme fraction 2 (CK-MB), BUN and creatinine, and decreased triglyceride, albumin, Ca2+, Na+, and K+).
Effects on the respiratory system (#B090393)	Male SD rats Single IV (over a period of 10 min) doses at 10, 20, 30 and 40 mg/kg (whole body plethysmography)	The respiratory rate for 1 minute (RR), tidal volume (TV), and minute volume (MV) were measured before and 1, 2, 4, 8, 24, and 48 hours after the start of administration. • 2 hr: no effects • 4 hr: ↑RR, TV and MV, dose-independent; ↑MV due to ↑RR and TV. • 8 hr: no significant changes • 24 hr: ↓RR (≥20 mg/kg), ↓MV (30 and 40 mg/kg) • 48 hr: ↓MV (40 mg/kg); indicating recovery at ≤30 mg/kg The biphasic changes, i.e., stimulating at 4 hours then suppressed at 24 hours and finally recovered by 48 hours at ≤30 mg/kg, occurred after Tmax (~10 minutes postdose). The effects possibly were not direct, rather secondary to the cytotoxicity of azacitidine.

Hemodynamic and ECG changes from Study #B071377 (Cardiovascular study; dogs)

Dose (mg/kg)	Blood Pressure (mmHg) Systolic	Diastolic	Mean	↑ HR (beats/min)	↓PR (msec)	↑QTc (msec)
2	Not remarkable	↑transient (4 hr postdose)	↑significant (4 hr postdose)	↑25-72 (4-6 hr postdose)	↓12-20 (4 hr postdose)	↑17-26 (4-8 hr postdose)
4	↓38 (24 hr postdose)	↓27 (24 hr postdose)	↓30 (24 hr postdose)	↑23-67 (2-24 hr postdose)	↓15-18 (4-8 hr postdose)	↑31-44 (4-24 hr postdose)
6	↓20-57 (4-48 hr postdose)	↓9-37 (24-48 hr postdose	↓42 (24 hr postdose)	↑30-84 (2-24 hr postdose)	↓16-32 (4-24 hr postdose)	↑10-46 (2-48 hr postdose)

Toxicokinetic parameters

Study #B071376 (CNS study; rats)

Dose (mg/kg)	C_{max} (ng/mL)	$AUC_{0\text{-}24hr}$ (ng*hr/mL)	T_{max} (hr)
10	6436	9826	0.17 (~10 min)
20	14138	20864	0.17
30	23375	34039	0.17
40	34050	54427	0.17

Study #B071377 (Cardiovascular study; dogs)

Recommended clinical dose		C_{max} (ng/mL) Oral 185 mg/m²	SC 75 mg/m²	IV 75 mg/m²		$AUC_{0\text{-}24hr}$ (ng*hr/mL) Oral 185 mg/m²	SC 75 mg/m²	IV 75 mg/m²
	Humans	145	750	2750	Humans	239	960	1044
Dose in dogs (mg/kg)/(mg/m²)	Dogs	Multiple			Dogs	Multiple		
2/40	2198	15.2	2.9	0.8	2454	10.3	2.6	2.35
4/80	7992	55.1	10.7	2.9	7180	30	7.5	6.9
6/120	7290	50.3	9.7	2.65	7379	30.9	7.7	7.1

Values below LLOQ (BLQ) were regarded as 0 ng/mL; Tmax: 10 minutes; multiple: animal/human exposures

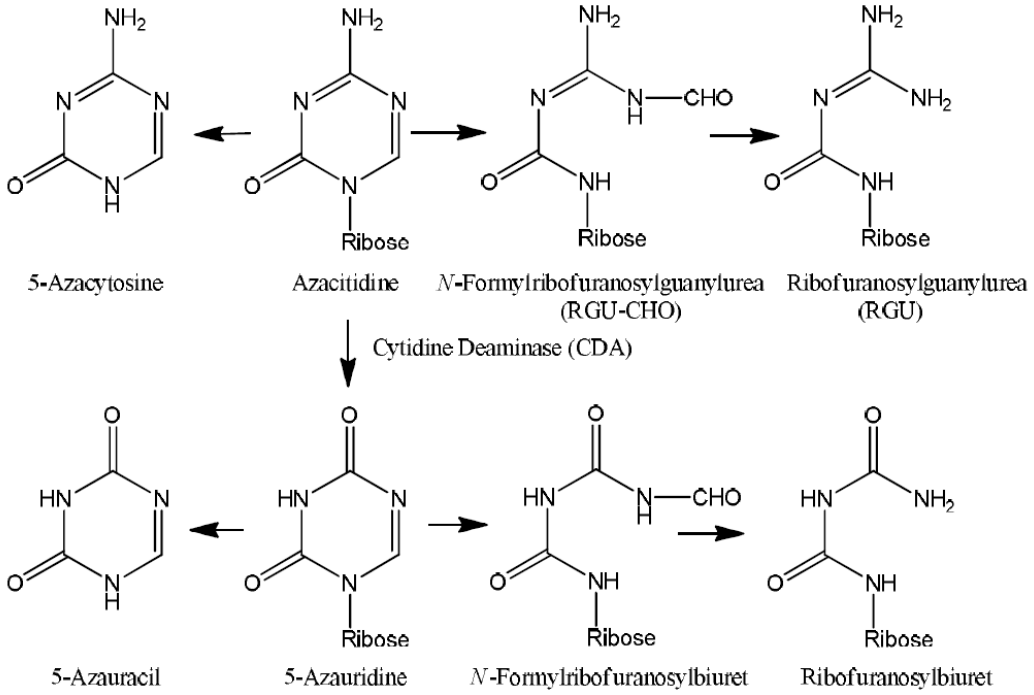
5.4 ADME/PK

Type of Study	Major Findings
Absorption	
Statement adapted from pharmacokinetic written summary* For Dog: Single dose: #AFZ0008-05-709; 5PHAMP3R2; 2-weeks: #1306-001	Azacitidine was rapidly absorbed in the mouse, rat, and dog following subcutaneous (SC) or oral (PO) administration. Subcutaneous bioavailability was greater than 70% in the rat and dog. Greater than 60% of the PO dose was absorbed and the oral bioavailability ranged from 22% to 38% in the mouse, rat, and dog. In dogs, following PO administration, azacitidine was rapidly absorbed, with the oral bioavailability at ~22%. Oral administration of azacitidine by drug-filled capsule or [redacted] (b) (4) tablet resulted in similar pharmacokinetic profiles. The $AUC_{0\text{-}4h}$ and C_{max} are comparable between the capsule group and the tablet group. A delay of absorption was observed in the tablet group relative to the capsule group (1.2 hours versus 0.67 hours). The systemic exposure was approximately dose-proportional and no accumulation was observed. T_{max}: 0.5 hours
Distribution	
In vitro serum protein binding of	^{14}C-azacitidine (0.1, 1 and 10 µg/mL) • Protein binding

Type of Study	Major Findings
14CNS-17 (#BP-NS17-090615) In vitro distribution ratio of 14C-NS-17 into human blood cells (#BP-NS17-100324)	In the absence of cytidine deaminase inhibitor tetrahydrouridine (THU): 7.42%-8.79% In the presence of THU: 5.54%-12.3% In vitro protein binding of azacitidine in human serum is low, protein binding is concentration dependent, and THU has no effect on protein binding. • Distribution into human blood cells In the absence of THU: 30.4-33.2% In the presence: 30.2-33.6% Distribution is concentration dependent and THU has no effect on distribution. • Blood-to-plasma exposure ratio: 1.1-1.8
Tissue distribution* #Azacitidine-DMOK-1401	Higher distribution to liver, spleen, bone marrow and thymus Azacitidine penetrated into the CNS and brain following PO and IV administration.
Bio-distribution** (#Azacitidine-DMPK-2808)	Objective: To compare two different dosing schedules [HELD/high dose and limited duration: 3 mg/kg, QD×5, or LEED/low dose and extended schedule: 1 mg/kg for 15 days (with 5 days on and 2 days off per week, for 3 weeks)] as measured by area under the curve (AUC) of [^{14}C] Aza incorporation into DNA/RNA in BM, and to correlate [^{14}C] Aza incorporation into DNA/RNA in whole blood (WB) or peripheral blood mononuclear cells (PBMC) vs. BM. Mice were treated intraperitoneally and clinical signs and blood samples were collected for PK/PD analyses. Administration of low dose and extended schedule conferred higher DNA (1.6- to 2.0-fold increase) and RNA (1.3- to 1.8-fold increase) incorporation of azacitidine in peripheral blood mononuclear cells and bone marrow of C57BL6 mice compared to a higher dose (3 mg/kg for 5 days) limited duration schedule, suggesting that azacitidine dose fractionation over an extended duration may increase both DNA and RNA incorporation.
Metabolism	
Statement adapted from pharmacokinetic written summary*	Azacitidine is not metabolized by CYPs. In vitro, azacitidine was not an inducer or inhibitor of CYPs at clinically relevant plasma concentrations. Azacitidine was neither a substrate nor an inhibitor of P-glycoprotein (P-gp).
Metabolites	Spontaneous hydrolysis of azacitidine is the major pathway in all species tested, and there were no unique human metabolites or degradation products. Spontaneous hydrolysis products: RGU-CHO and RGU. Hydrolytic degradation of azacitidine results in formation of 5-azacytosine and 5-azauracil. Deamination, mediated by the enzyme cytidine deaminase is the primary pathway for the breakdown of azacitidine to 5-azauridine. Major metabolites in circulation: M1 and M10 (RGU) Major metabolites in urine and feces: M1, M10, and M6 See metabolism pathway below.
Excretion	
Statement adapted from pharmacokinetic written summary*	Mouse, rat, and dog: major route of elimination is urinary
Toxicokinetics	See TK data in respective toxicology studies below.

*Source study: #7781-115 (b) (4)
RGU-CHO: N-formylribofuranosylguanylurea; RGU: Ribofuranosylguanylurea
**Source study: [^{14}C] Azacitidine distribution in blood and intracellular incorporation in peripheral blood mononuclear cells and bone marrow after multiple intraperitoneal administration to male C57BL/6 mice

Figure 6: Summary of Azacitidine Metabolism Pathways and Metabolites



(Figure from the Applicant)

5.5 TOXICOLOGY

5.5.1 General Toxicology

The toxicology studies used to support the approval of VIDAZA were administered via the intraperitoneal route. These data reviewed under NDA 050794 are cross-referenced for the current NDA submission. The safety profile of oral azacitidine (CC-486) was assessed in the toxicology studies reviewed below.

Study title/ number: Azacitidine: A 2-week oral toxicity study in dogs with 3-week recovery (Study #1306-001)

Key Study Findings:

- Orally administered azacitidine (CC-486) was tolerated up to 0.2 mg/kg/day (4 mg/m^2/day) when given daily for 14 days.
- Mortality and cytotoxic effects were mainly due to myelosuppression of the bone marrow. The target organs included the bone marrow, lymphoid organs, GI tracts and liver. The toxicities were mostly un-recoverable.
- Oral azacitidine exhibited comparable toxicities as azacitidine via injection.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Test article: Azacitidine (Lot # 050017; purity: 99.6%)

Methods

Dose and frequency of dosing:	0, 0.2, 0.4 or 0.8 mg/kg/day (Groups 1, 2, 3 and 4, respectively). Animals were treated once daily for up to 14 days. Group 4 dogs were dosed for 10 days.
Route of administration:	Oral
Formulation/Vehicle:	(b) (4) tablet/placebo tablets for control group and gelatin capsules for azacitidine-treated groups
Species/Strain:	Dogs/beagle
Number/Sex/Group:	5/sex/group [dosing (main study) group: 3/sex/group; drug free (recovery) group: 2/sex/group]
Age:	144-152 days
Weight:	5.38-7 kg
Satellite groups/ unique design:	A fifth group received a fixed dosage of 5 mg azacitidine/animal/day by (b) (4) tablet once daily for 10 days. Animals were selected for the study based on body weight to ensure that the fixed dose of 5 mg/animal/day resulted in an initial daily dose of approximately 0.8 mg/kg/day.
Deviation from study protocol affecting interpretation of results:	Groups 4 and 5 were dosed for only 10 days due to adverse toxicity and were drug free after Day 10 (as recovery period) until euthanized. Due to body weight losses observed during the study, the actual dosages administered may have been higher than the nominal or targeted dosages.

Observations and Results: changes from control

Observations for mortality, morbidity, injury, and the availability of food and water were conducted twice daily for all animals.

Parameters	Major findings
Mortality Scheduled necropsy: Day 15 (main study group) and Day 38 (recovery group)	0.4 mg/kg/day: 1 (found dead)/5M on Day 23 (RD 9); 2 (found dead or euthanasia)/5F on Day 20 (RD6). 0.8 mg/kg/day: all dogs did not survive; they were euthanized or found dead (from Day 1: between 10-16 days for males and 10-20 days for females) 5 mg/day: all dogs did not survive; they were euthanized or found dead (between 9-15 days from Day 1) 0.8 mg/kg/day: all dogs did not survive; they were euthanized or found dead (from Day 1: between 10-16 days for males and 10-20 days for females) 5 mg/day: all dogs did not survive; they were euthanized or found dead (between 9-15 days from Day 1) Duration of recovery period (pooled M+F)

	Control*	0.2 mkd	0.4 mkd	0.8 mkd	5 mg/d*
Average	24 D	24 D	9.25 D	4.75 D	3.25 D
(Range)			(6-16 D)	(3-6 D)	(2-5 D)

mkd: mg/kg/day, D; day; *tablets; RD: recovery day

<table>
<tr><td></td><td>Causes of death: mainly due to bone marrow depletion and the associated inflammation.</td></tr>
<tr><td>Clinical Signs</td><td>Observed twice daily.
0.2 mg/kg/day: fecal changes; recoverable
0.4 and 0.8 mg/kg/day and 5 mg/day: fecal changes, decreased activity, hunched posture, lateral recumbency, inappetence, thin, and discoloration of the gum; adverse and not recoverable</td></tr>
<tr><td>Body Weights and food consumption</td><td>Measured on Days -1/1, 7, 13, 14, 17, 21, 24, 28 and 34/35.
Adverse body weight reduction mainly at ≥ 0.4 mg/kg/day

Body weight: absolute weight
<table>
<tr><th></th><th colspan="2">Predose</th><th colspan="2">Week 1</th><th colspan="2">Day 14</th><th colspan="2">Recovery</th></tr>
<tr><th></th><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th></tr>
<tr><td>0.4 mkd</td><td>NC</td><td>NC</td><td>-8</td><td>-4</td><td>-13</td><td>-9</td><td>-23</td><td>-25</td></tr>
<tr><td>0.8 mkd</td><td>NC</td><td>NC</td><td>-13</td><td>-14</td><td>-20 (D13)</td><td>-22 (D13)</td><td>NA</td><td>NA</td></tr>
<tr><td>5 mg/d</td><td>NC</td><td>NC</td><td>-15</td><td>-16</td><td>-23 (D13)</td><td>-23% (D10)</td><td>NA</td><td>NA</td></tr>
</table>
Data expressed as percent reduction from the concurrent control (93% of the control would be -7%); NC: no change, 100% of control; NA: not applicable, animals were euthanized.

Food consumption
<table>
<tr><th></th><th colspan="2">Week 1</th><th colspan="2">Day 14</th><th colspan="2">Recovery</th></tr>
<tr><th></th><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th></tr>
<tr><td>0.4 mkd</td><td>-38</td><td>-12</td><td>-26</td><td>-20</td><td>-86</td><td>NA</td></tr>
<tr><td>0.8 mkd</td><td>-68</td><td>-66</td><td>NA</td><td>-88</td><td>NA</td><td>NA</td></tr>
<tr><td>5 mg/d</td><td>-80</td><td>-80</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td></tr>
</table>
Data expressed as percent reduction from the concurrent control
NA: not available, the data measurement required at least two survivors during the interval.

Adverse reduction in food consumption correlated with body weight reductions in the affected animals. The findings may be attributed to the GI effects of azacitidine.</td></tr>
<tr><td>Ophthalmoscopy</td><td>Once prior to start of dosing, prior to necropsies and once during recovery in Week 4

Not remarkable</td></tr>
<tr><td>ECG</td><td>Prior to the start of dosing and on Day 14; ≤ 0.4 mg/kg/day: prior to dosing and 1-2 hours after dosing; Group 4 and 5 mg/day: a single examination.

Not remarkable</td></tr>
<tr><td>Hematology and coagulation</td><td>Blood sampling was conducted prior to the start of dosing, on Day 14, and on Days 24, 30, 34 and/or 38 during the recovery period. Also, on Day 10 and in euthanized animals.

Hematology: Treatment related pancytopenia was observed in all treated dogs, mainly suppression of leukocytes, lymphocytes, neutrophils, monocytes, eosinophils, basophils, large unstained cells</td></tr>
</table>

	(LUC), reticulocytes (absolute and percent), and platelets (Day 14). During the recovery period, re-bounded counts were noted in the surviving animals. No remarkable effects were observed in erythroid parameters. The myelosuppression and leukopenia effects correlated with bone marrow hyperplasia and lymphoid depletion in the thymus, spleen and lymph nodes. Coagulation: Prolonged aPTT correlated with thrombocytopenia (decreased platelets) and red discoloration (macroscopic finding) and hemorrhage (microscopic finding) observed in multiple organs. The findings were not recovered in surviving animals at the end of the recovery period.
Clinical Chemistry	See "Hematology and coagulation" for sampling times. ↓serum K+ and Phosphorus: corresponding
Urinalysis *[delete the row if not evaluated]*	Urine samples were collected for at least 16 hours on Day 14 during the dosing period, and on Days 24, 30, 34 and/or 38 during recovery period. Increased protein levels in the urine on Day 14 0.8 mg/kg/day: 1M and 2F 5 mg/kg/day: 2M
Gross Pathology	Dosing period: Small thymus: mild, 1F at 5 mg/day; correlated with lymphoid depletion Recovery period: • Small thymus: mild, ≥ 0.4 mg/kg/day in males and 0.8 mg/kg/day in females • Depletion of body fat: mild, 1M and 1F at 0.8 mg/kg/day and 2F at 5 mg/day; correlated with serious atrophy of fat in the bone marrow and body weight reductions. • Occasionally erosions in the large intestine were noted (0.8 mg/kg/day and 5 mg/day females).
Organ Weights	Dosing period Decreased thymus weights were observed at all dose levels in both males (46%-64%) and females (20%-37%) compared to the controls; correlated with lymphoid depletion in the thymus. The finding was recovered at 0.2 mg/kg/day. The following organ weights changes were considered secondary to decreased body weights: ↑ brain to body weight (0.8 mg/kg/day males), ↓ kidney and liver weights (5 mg females). Recovery period Thymus weight reduction was seen in the recovery necropsy at all dose levels with increased severity in comparison with the finding following the dosing period. Decreased thymus weights (% reduction from the control) 0.2 mg/kg/day — 0.4 mg/kg/day — 0.8 mg/kg/day Males: 42% — 90% — 87% Females: 30% — 84% — 83%

Histopathology **Adequate battery:** Yes	Dosing period (terminal necropsy) • Bone marrow: ≥0.2 mg/kg/day Minimal to severe (dose-dependent increases in severity) mixed cellular depletion in the rib, femur and sternum • Liver: 0.8 mg/kg/day and 5 mg/day Minimal to moderate centrilobular hepatocellular vacuolation • Spleen: 0.8 mg/kg/day and 5 mg/day Minimal to mild lymphoid depletion • Thymus: lymphoid depletion Minimal to severe (dose-dependent increases in severity) • Mandibular salivary glands: 0.8 mg/kg/day and 5 mg/day Decreased secretory product; may be secondary to body weight reductions Recovery period • Bone marrow depletion: Mild in the sternum only (no findings in the rib or femur) in the 0.2 mg/kg/day dogs; reduced severity indicating signs of recovery. No signs of recovery at ≥ 0.4 mg/kg/day (early deaths) • Lymphoid depletion: ≥ 0.4 mg/kg/day Increased severity in spleen (mild to moderate) and thymus (mild to severe); mesenteric lymph node (mild) in 0.8 mg/kg/day and 5 mg/day males and 0.4 and 0.8 mg/kg/day females • Small and large intestines: 0.8 mg/kg/day males and 0.4 mg/kg/day females Minimal to mild gland/lumen dilatation and single cell necrosis; the findings were consistent with minor irritation of the intestine which were not observed at terminal necropsy. The findings were also likely a secondary result of bacterial infection following decreased disease resistance caused by bone marrow and lymphoid depletion.
Bone marrow smears	For all animals, samples were evaluated microscopically and the parameters included the proportions of erythroid and granulocytic maturation stages, as well as total erythroid, granulocytic, and lymphoid cells, and myeloid:erythroid (M:E) ratios. Bone marrow cytology findings: At ≥0.4 mg/kg/day: rare or no presence of erythroid or myeloid marrow cells, rare presence of megakaryocytes, increased marrow lipid, and the presence of fibroblasts suggesting myelofibrosis. Predominant cells found were fibroblasts and marrow stromal cells, with occasional lymphocytes. M:E ratio was not determined at ≥0.4 mg/kg/day. At 0.2 mg/kg/day: increased lipid, decreased cellularity, increased lymphocytes and large spindle cells. These findings in the bone marrow cytology resolved. Decreased M:E ratio compared to the control was attributable to the marked decreases in mature neutrophils and increased numbers of cells of immature granulocytic stages; the M:E ratios showed recovery. M:E ratios

	Control		0.2 mg/kg/day	
	Males	Females	Males	Females
Terminal	1.5	1.4	0.4*	0.7
Recovery	1.4	1.4	2.6	0.8

*Increased total erythroid cells versus control: 53.6% versus 39.7%, contributing partly to decreased M:E ratio.

M: males; F: females
↓: indicates reduction in parameters compared to control.

Toxicokinetics:

Blood samples (approximately 2 mL, from jugular vein) were collected from all animals on Day 1 (predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 10 hours postdose), animals at 0.8 mg/kg/day and 5 mg/animal/day on Day 10 (predose and 0.5, 1, 1.5 and 2 hours postdose), and from animals at 0 (placebo), 0.2, and 0.4 mg/kg/day on Day 14 (same time points as Day 1). LLOQ (lower limit of quantification): 0.025 µg/mL.

Table 2: Toxicokinetic Parameters (2-Week Oral Toxicology Study in Dogs)

Parameters	0.2 mg/kg[a]		0.4 mg/kg[a]		0.8 mg/kg[a]		5 mg/animal/day[b]	
	Male	Female	Male	Female	Male	Female	Male	Female
Day 1								
C_{max} (ng/mL)	119	168	175	207	721	583	657	795
T_{max} (hr)	0.903	0.900	0.800	0.907	0.817	0.703	1.10	1.01
AUC_T (hr·ng/mL)	178	237	269	306	1040	907	932	1000
AUC (hr·ng/mL)	222	273	319	342	1090	967	1000	1080
$T_{1/2}$ (hr)	0.977	0.782	1.10	0.862	0.767	0.781	0.836	0.844
Day 10 (0.8 mg/kg/day and 5 mg/animal/day) or Day 14 (0.2 mg/kg/day and 0.4 mg/kg/day)								
C_{max} (ng/mL)	129	152	251	313	880	761	1080	744
T_{max} (hr)	0.600	0.703	0.803	0.707	0.600	0.746	1.13	1.13
AUC_T (hr·ng/mL)	148	223	344	478	997	971	756	823
AUC (hr·ng/mL)	168	239	362	501	1320	1330	885	1170
$T_{1/2}$ (hr)	0.821	0.993	0.792	0.883	0.829	0.843	0.709	0.837

AUC_T – Area under the concentration-time curve (AUC) calculated from time zero to the last observed concentration
[a]administered as a capsule (API filled)
[b]targeted 0.8 mg/kg/day dose administered as a fixed 5 mg/animal/day (b) (4) tablet
(Table from the Applicant)

General toxicology; additional studies

Mouse

The following study in mice was reviewed and summarized.

Study title: Preclinical toxicology NSC 102816 (5-azacitine) in mice, hamsters and dogs (Study # PH-43-65-61; Experiment facility: (b) (4))

The oral azacitidine toxicities were investigated in mice via single and repeated dose administrations. Swiss mice (n=10/sex/group) were administered azacitidine (water as vehicle) via a single orally-intubated dose (431-750 mg/kg; 1293-2250 mg/m^2) or once daily for 5 days (3-6 mg/kg or 9-18 mg/m^2;administration volume 0.9-1.5/20 g body weight). The single-dose oral LD_{50} calculated was approximately 572.3 mg/kg (1717 mg/m^2). At ≥1557 mg/m^2, there was decreased liver weight correlating with depleted glycogen deposits. In the 5-day repeated dose study, the LD_{10}, LD_{50} and LD_{90} were calculated to be approximately 9, 13 and 18 mg/m^2, respectively. No MTD was identified. Decreased mean body weight and decreased activity were observed at ≥10.6 mg/m^2/day. Decreased glycogen content and fatty changes in the liver and renal tubular degeneration were observed in some animals at all azacitidine dose levels.

Dogs

Study title: Azacitidine: a 2-day oral tolerability and pharmacokinetic study in dogs (Study #1306-002; Testing facility: (b) (4))

Two groups of three female beagle dogs were administered azacitidine (0.8 mg/kg/day; 16 mg/m^2/day) in a capsule or as a 5 mg (b) (4) tablet. No mortality occurred in this study. All animals showed non-adverse emesis and mucoid feces plus a minimal reduction in body weight and decreased food consumption. Mean exposures ($AUC_{0\text{-}4hr}$) of 780 and 690 ng·hr/mL were obtained with the capsule and tablet formulations, respectively. Both dose levels were considered MTDs in this study.

5.5.2 Genetic Toxicology

The genetic toxicology studies used to support the approval of VIDAZA are cross-referenced.

5.5.3 Carcinogenicity

The carcinogenicity studies used to support the approval of VIDAZA were administered via the intraperitoneal route. The data are cross-referenced.

5.5.4 Reproductive and Developmental Toxicology

The reproductive and developmental toxicology studies used to support the approval of VIDAZA were administered via the intraperitoneal route. The data are cross-referenced.

The tables below provide the estimation of exposure multiples (rodents versus humans) for reproductive/teratogenic and carcinogenicity effects of oral azacitidine (Sections 8 and 13 of Labeling)

Table 3: Exposure Multiples: Embryofetal and Developmental Toxicities

	Early embryotoxicity	Developmental abnormality (brain)	Embryotoxic	Fetal death and abnormalities
Rodents (mg/m^2)	6 (IP, mice)	3 to 12 (IP, mice)	6 (IP, rats)	3 to 12 (IP, rats)
Humans (mg/m^2)	75 (IV)/185 (PO)	75 (IV)/185 (PO)	75 (IV)/185 (PO)	75 (IV)/185 (PO)
Multiples (%) Rodent (IP)/human (IV)	8%	4 to 16%	8%	4 to 16%
Multiples (%) Rodent (IP)/human (PO)	3%	1.6 to 6.5%	3%	1.6 to 6.5%

Multiples: ratio of rodent exposure/human exposure (on BSA basis) x100%; human: recommended dose via IV or SC: 75 mg/m^2; oral 300 mg (185 mg/m^2 for a 60 kg human subject).

Table 4: Exposure Multiples: Carcinogenicity and Male Fertility

	Carcinogenicity		Male Fertility	
Rodents (mg/m^2)	6 to 6.6 (IP, mice)	15 or 60 (IP, rats)	9.9 (IP, mice)	15 to 30 (IP, rats)
Humans (mg/m^2)	75 (IV)/185 (PO)	75 (IV)/185 (PO)	75 (IV)/185 (PO)	75 (IV)/185 (PO)
Multiples (%) Rodent (IP)/human (IV)	8 to 8.8%	20 to 80%	13%	20 to 40%
Multiples (%) Rodent (IP)/human (PO)	3 to 3.6%	8 to 32%	5.4%	8 to 16%

Multiples expressed as: rodent exposure/human exposure (on BSA basis) x100%; human: recommended dose via IV or SC: 75 mg/m^2; oral 300 mg (185 mg/m^2 for a 60 mg human subject).

Conclusions

- The assessments of embryofetal and developmental toxicities, male fertility and carcinogenicity of azacitidine in rodents were conducted via the intraperitoneal and not the oral route.

- The rodent to human exposure multiples (based on body surface area/BSA basis) are less than 10% in most cases when compared to the exposure at the recommended human doses administered intravenously/subcutaneously or orally.

- Taking into consideration the low oral bioavailability of azacitidine in humans (11%), the actual exposure ratios between rodent (IP) to human (oral) would be different than the % values presented in the tables above that were based on body surface area (mg/m^2) without incorporating the bioavailability concerns.

The assessments of embryofetal and developmental toxicities, male fertility and carcinogenicity of azacitidine in rodents were not conducted via the oral route. The exposure multiples based on BSA were expressed in percentage (%) of human exposure in Sections 8 and 13 of the VIDAZA labeling (i.e., rodent exposure via IP route versus human exposure of injectable azacitidine). In order to include the comparisons to the human exposures at the recommended oral (ONUREG) and injectable (VIDAZA) doses, only a general description instead of % values is

used in the ONUREG labeling in Section 8 and Section 13 (male fertility). The exposure multiples for the carcinogenicity evaluation are expressed as exposure ratio (%) of rodent (IP) versus human injectable azacitidine.

5.5.5 Other Toxicology Studies

Qualification of impurities

Drug Substance

The impurities in the drug substance are [redacted] (b) (4) the specification for individual impurities is NMT [redacted] (b) (4) % (w/w) [redacted] (b) (4) [redacted] (b) (4) The specification and justification of the specification for the drug substance in Vidaza (NDA 050704, SN0097 and SN0080, respectively) are cross-referenced.

Drug product

The CC-486 drug product typically has [redacted] (b) (4) The structure and the source of the CC-486 degradation products are shown in the table below.

Table 5: Summary of Impurities/Degradants in Drug Product

Impurity	Description	Specification	Comment
[redacted] (b) (4)			[redacted] (b) (4) In xenografted mice bearing L1210 leukemia cells (n=10/group, IP on Days 1, 5 and 9), RGU-CHO showed 1/4 the anti-tumor effect of azacitidine, but was comparably much less toxic (↓ body weight). In this study, the determined NOAEL for IP administration was 240 mg/kg/day Q4D (equivalent to 60 mg/kg/day of azacitidine) in mice (HED: 19.5 mg/kg, or 720 mg/m^2 Q4D, or approximately 420 mg/kg/week or 1260 mg/m^2/week). Mutagenic Mutagenic

(b) (4)	Qualified at oral daily doses 1.23 mg/kg and 0.62 mg/kg (HED 3.7 mg/m^2 and 1.86 mg/m^2) for male and female mice, respectively. IV administrations in mice were tolerated up to 1.26 mg/kg/day (3.78 mg/m^2) for 7 days. Mice were treated orally with (b) (4) and no acute toxicities were found up to 30 or 45 mg (or ~1200-1800 mg/kg; ~3600-5400 mg/m^2) per day for 4-14 days

DS: drug substance; DP: drug product

Table 6: Acceptance Criterion versus Qualified Limits of Degradants in Drug Product

(b) (4)

As indicated in the table, the proposed acceptance criteria (b) (4) of azacitidine is much lower than the qualified limits.

Conclusion
The proposed specification limits (% w/w) of the impurities are acceptable based on the ICH Q3A and Q3B guidances, qualification in toxicology studies, or the levels present in the azacitidine drug substance or drug product for Vidaza.

Qualification of degradants of drug product CC-486 (oral azacitidine)

- (b) (4)

Study title/ number: (b) (4) A 21-Day Repeat Dose Oral Gavage Toxicity Study in Mice (Study # Azacitidine-TOX-2756; (b) (4) Number KB81SN)

Key Study Findings:

- Oral (b) (4) was tolerated up to 1.23 mg/kg/day (3.7 mg/m^2/day) in males and 0.62 mg/kg/day (1.86 mg/m^2/day) in females. At these NOAELs, the corresponding Day 14 AUC_{last} levels were 696 ng*hr/mL for males and 218 ng*hr/mL for females.

- This study was used to qualify the impurity (b) (4) at a dose of 1.86 mg/m^2/day.

- At 1.23 mg/kg/day, females were pseudopregnant based on microscopic changes in the reproductive organs/tissues.

- Changes in reproductive organs were considered adverse because of its potential impact on reproductive ability during the (b) (4) treatment period.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes
Test article: (b) (4) Batch #7650-7-C

Methods

Dose and frequency of dosing:	0 (deionized water), 0.31, 0.62 or 1.23 mg/kg/day*, once daily for 21 days. *As Groups 1, 2, 3 and 4, or control, LD, MD and HD, respectively.
Route of administration:	Oral gavage (10 mL/kg)
Formulation/Vehicle:	Deionized water (Batch # DDW0063)
Species/Strain:	Mouse/CD-1 mice
Number/Sex/Group:	21-day main study: 10/sex/group 14-day TK: 18/sex/group, except for control (3/sex)
Age:	10 weeks
Satellite groups/ unique design:	Toxicokinetics
Deviation from study protocol affecting interpretation of results:	Not remarkable

Observations and Results: changes from control
All animals were observed for mortality and general condition twice daily, prior to dosing and 1-2 hours after dosing. For clinical pathology parameters, blood samples were obtained via the vena cava prior to necropsy.

Parameters	**Major findings**
Mortality	Not remarkable
Clinical Signs	Not remarkable
Body Weights and food consumption	Twice predose and twice weekly Changes in body weight were mainly observed in females at 1.23 mg/kg/day (HD) on Day 22: • Absolute weight: ↑11.6% from the control • Weight gain: ↑6.5% from Day 1 • Weight gains were attributable to females with pseudopregnancy and associated with increased food intake. Increased food consumption was observed in all treated females beginning on Day 8, especially at HD.

<table>
<tr><td>Ophthalmoscopy</td><td>Not remarkable</td></tr>
<tr><td>Hematology</td><td>Main findings were increased total and differentiated white counts in females:

<table>
<tr><td></td><td colspan="4">Mean (fold change versus concurrent control)</td></tr>
<tr><td>Dose mkd</td><td>0</td><td>0.31</td><td>0.62</td><td>1.23</td></tr>
<tr><td>WBC*</td><td>4.07</td><td>NR</td><td>NR</td><td>7.97** (1.96)</td></tr>
<tr><td>Lymphocyte</td><td>2.84</td><td>4.98** (1.75)</td><td>4.04** (1.42)</td><td>6.29** (2.21)</td></tr>
<tr><td>Monocytes</td><td>0.07</td><td>NR</td><td>NR</td><td>0.16** (2.29)</td></tr>
<tr><td>LUC</td><td>0.02</td><td>NR</td><td>NR</td><td>0.06** (3.00)</td></tr>
</table>
Mkd: mg/kg/day; *unit: x 10E3/µL; LUC: large unstained cells; NR: not remarkable; ** statistically significant changes (p<0.05)</td></tr>
<tr><td>Clinical Chemistry</td><td>Not remarkable</td></tr>
<tr><td>Gross Pathology</td><td>Enlarged spleen observed in 4/10 HD females.
The finding was correlated with increased extramedullary hematopoiesis, a sign attributable to pseusopregnancy or other estrous cycle variations.[56]</td></tr>
<tr><td>Organ Weights</td><td>Significantly increased weights in the ovaries and spleen observed in HD females.
Organ weights (% increase versus concurrent control)
<table>
<tr><td></td><td>Absolute (%)</td><td>Vs. Body weight (%)</td><td>Vs. Brian weight (%)</td></tr>
<tr><td>Ovaries*</td><td>50</td><td>35</td><td>37</td></tr>
<tr><td>Spleen</td><td>52</td><td>36</td><td>41</td></tr>
</table>
*mainly in 3/10 females
Increased ovary weights correlated with increased corpora lutea in 3/10 HD females. The increases in these animals were enough to achieve statistically significant increases in the group means.</td></tr>
<tr><td>Histopathology
Adequate battery: Yes</td><td>Peer review: Applicant-designated peer review pathologist

Not remarkable, except for the findings in female mice: Histopathological changes observed in vagina, uterus/cervix, and mammary gland. Increased ovarian weights in HD females were consistent with pseudopregnancy

The pathologist's evaluation and conclusion of pseudopregnancy was reviewed. The reviewer concurred with the pathologist.
See Table below.</td></tr>
<tr><td>Toxicokinetics</td><td>Blood samples for TK (~0.6 mL) were obtained from the toxicokinetic study animals on Day 14 from control group (3 animals/sex) at 1 hour post dose and from treated groups (3 animals/sex/timepoint) at 0.5, 1, 2, 4, 6, and 12 hours post dose.</td></tr>
</table>

LD: low dose; MD: mid dose; HD: high dose.

[56] Norton et al., Biol Reprod 81(3): 457-464, 2009.

Table 7: Histopathological findings in female mice (b) (4)

Group/sex	1F	2F[a]	3F[a]	4F
Dose (mg/kg/day)	**0**	**0.31**	**0.62**	**1.23**
Vaginal Mucification				
Minimal	0	1	1	5
Total	0	1	1	5
Uterine Epithelial Hypertrophy				
Minimal	0	1	1	5
Total	0	1	1	5
Ovarian Increased Corpora Lutea				
Minimal	0	1	1	3
Total	0	1	1	3
Mammary gland lobular hypertrophy/hyperplasia				
Minimal	0	1	1	5
Total	0	1	1	5
Increased Extramedullary Hematopoiesis				
Minimal	0	0	2	3
Slight	0	1	0	2
Total	0	1	2	5
Number of animals / tissues examined	10	10	10	10

F= female

[a] Findings in the female reproductive tract and spleen were not related to (b) (4) in these groups[57]

(Table from the Applicant)

According to Ryan and Schwartz, spontaneous pseudopregnancy may occur with increased incidence (25% of cycles) in small group-housed females. The findings of the reproductive tract and spleen related to pseudopregnancy observed in one female at 0.31 mg/kg/day and one female at 0.62 mg/kg/day were therefore considered well within the range of spontaneous occurrence, and unrelated to (b) (4)

[57] Ryan and Schwartz, Biology of Reproduction 17: 578-583, 1977.

Table 8: Toxicokinetic parameters (b) (4)

	Males			Females		
Dose (mg/kg/day)	0.31	0.62	1.23	0.31	0.62	1.23
Day 14						
C_{max} (ng/mL)	106	193	372	70.6	132	260
AUC_{LST} (ng•hr/mL)	186	302	696	129	218	504

AUC_{LST} = area under the plasma concentration-time curve from time zero to the last quantifiable plasma concentration; C_{max} = maximum plasma concentration.

The following studies were reviewed, and the study reports are summarized.

Study title: (b) (4) A 7-day intravenous (slow bolus) injection study in mice (Study # Azacitidine-TOX-2918; test facility study number: YM26YB; GLP compliant)

Intravenous doses of 0.63 and 1.26 mg/kg/day (b) (4) administered to mice for 7 days were tolerated. The findings at ≥ 0.63 mg/kg/day included minimal to mild increases in lymphocytes with corresponding increases in total white blood cells, minimal increases in platelets (females only), mild increases in triglycerides (males only), and minimal increases in total calcium. The findings were non-adverse, thus the NOAEL was 1.26 mg/kg/day, corresponding to a combined sex AUC_{LST} of 2060 ng*h/mL.

Study title: A 7-day intravenous (bolus injection) toxicity study of Vidaza (azacitidine for injection) and related degradants (b) (4) in mice followed by a 7-day drug free period (Study # Vidaza-TOX-1475; test facility study number 12-2307; GLP compliant)

Vidaza (Batch # 7K008 or 11435) administered intravenously to CD-1 mice (15/sex/group) at 3 mg/kg/day, without or with (b) (4) (0.045 mg/kg/day or 0.09 mg/kg/day, i.e., 1.5% w/w or 3% w/w of Vidaza) for 7 days, followed by a 7-day drug-free period. Vidaza resulted in the expected cytotoxic effects, mainly the suppression of the lymphohematopoietic system. (b) (4) in combination with Vidaza did not alter this toxicity. At the end of a 7-day drug-free period, there was partial to complete recovery for all changes with the exception of decreased red cell mass (males), lymphocytes (both sexes), and cholesterol (females) in animals previously administered Vidaza with or without (b) (4) In conclusion, (b) (4) up to 3% w/w did not alter Vidaza-related toxicity in mice.

- (b) (4)

Article title: Effect of (b) (4) on the growth of mice (b) (4)

Background

The following is excerpted from the article:

Mice were treated (b) (4) via oral gavage at 30 or 45 mg (or ~1200-1800 mg/kg; ~3600-5400 mg/m^2) per day for 4-14 days. No remarkable changes in food consumption or body weight changes were noted. While no changes in glutamic-oxaloacetic transaminase (GOT) and lactate dehydrogenase (LDH) enzymes were reported at 30 mg/day, treatment with 45 mg/day induced significantly lower LDH and GOT activity levels. On the other hand, dietary administration (b) (4) (3% (b) (4) in the diet) resulted in decreased food consumption, weight loss, and death of one mouse. An additional food selection study confirmed that food consumption was discouraged when (b) (4) levels were greater that 0.25% in the diet. The findings resolved with the supplement of sucrose or vanilla essence. Examination of eyes from (b) (4)-treated mice by stereomicroscopy revealed no evidence of the blinding effect that was seen previously in mice.

6 CLINICAL PHARMACOLOGY

6.1 EXECUTIVE SUMMARY

ONUREG is an oral dosage form of azacitidine, a nucleoside metabolic inhibitor. The Applicant is seeking approval of ONUREG (b) (4) The proposed dosing regimen is 300 mg orally once daily (QD) with or without food on Days 1 to Day 14 of each 28-day cycle.

The clinical pharmacology properties of azacitidine as injectable forms (IV or SC) were previously characterized and described in the market application of Vidaza® (approval in 2004). The present clinical pharmacology program of oral azacitidine (CC-486) focused on the examination of PK characteristics following oral administration as well as biopharmaceutic evaluation, including food effect and bioequivalence assessment in support of formulation development (AZA-MDS-004 and CC-486-CAGEN-001). A population PK (popPK) analysis was conducted to identify the sources of PK variability, including evaluation of the effects of hepatic and renal impairment on the PK of azacitidine. Reports of exposure-response (E-R) analyses for efficacy and safety were also included in the current NDA submission.

The mean exposure (AUC_∞) after oral azacitidine at 300 mg was ~25% of that following subcutaneous (SC) administration of 75 mg/m^2 azacitidine (244 ±126 vs. 1021 ± 400 ng.h/mL). There was no clinically relevant effect of a high-fat, high-calorie meal or gastric acid reducing agents (ARA) on azacitidine absorption. Azacitidine is primary metabolized via spontaneous hydrolysis and deamination by cytidine deaminase, followed by renal excretion. Renal excretion represents a minor elimination pathway of parent drug with < 2% of oral dose excreted unchanged. The popPK analysis of azacitidine did not identify covariates that are of clinical significance. No dose adjustment is recommended in patients with mild hepatic impairment or mild to severe renal impairment. The effect of moderate or severe hepatic impairment on azacitidine exposure and safety has not been studied and a postmarketing clinical study will be needed to address this issue. The risk of CYP- and drug transporter-mediated DDI is low with azacitidine as a victim or perpetrator based on in vitro interaction potential. There was no report of any QTc prolongation event in the present clinical program following oral administration of azacitidine and concentration-QTc analysis was not conducted.

The proposed dosing regimen of 300 mg orally, QD for the first 14 days of a 28-day cycle, was evaluated in the randomized, placebo-controlled, double-blinded study CC-486-AML-001 to support efficacy in AML patients who had achieved CR / CRi with induction chemotherapy ± consolidation. The exposure-response (E-R) analyses suggested a positive trend for efficacy (OS and RFS). Azacitidine exposure was predictive for the occurrence of Grade 3/4 neutropenia and probability of dose reduction to 200 mg QD for 7 or 14 days due to AEs. Given the overall

benefit/risk, the recommended dosing regimen of azacitidine 300 mg QD and dosage modifications in the event of adverse reactions is acceptable from a clinical pharmacology standpoint.

Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 214120. This NDA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The primary evidence of effectiveness was from study CC-486-AML-001 in the intended patient population. The median OS (95% CI), the primary efficacy endpoint, was 24.7 months (18.7, 30.5) in patients treated with azacitidine 300 mg QD for the first 14 days of a 28-day cycle vs 14.8 months (11.7, 17.6) in the placebo arm.
General dosing instructions for adults	The recommended dosing regimen is azacitidine 300 mg QD with or without food for the first 14 days of a 28-day cycle.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• No dose adjustment is recommended for patients with mild hepatic impairment. The effect of moderate or severe hepatic impairment on azacitidine exposure is unknown. A PMR is to be issued for conducting a hepatic impairment study to determine appropriate dose(s) for this specific patient population. • No dose adjustment is recommended for patients with mild to severe renal impairment.
Bridging between the to-be-marketed formulation and clinical trial formulations	Among the three primary (b) (4) tablet formulations (F6, F8 and F9), the registration trial CC-486-AML-001 used F8. The bioequivalence of F8 (150 mg x 2) and F9 (300 mg) was demonstrated in study CC-486-CAGEN-001. F9 is the intended commercial formulation (ICF), with the only difference between F9 and ICF being the addition of the commercial image. ONUREG will be supplied as 200 and 300 mg tablets. There is no difference on dissolution rate at pH 1 to 6.8 between F9 300 mg vs. ICF 300 mg vs. ICF 200 mg.
Labeling	Revisions were incorporated in Section 8 Specific Populations and Section 12 Clinical Pharmacology of the proposed labeling.

Postmarketing Requirements and Commitments

PMC or PMR	Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features
PMR	Identify azacitidine dose in patients with moderate and severe hepatic impairment	Azacitidine undergoes hepatic metabolism mediated by cytidine deaminase. Increased hepatoxicity was previously reported for Vidaza® in patients with pre-existing severe hepatic impairment. There is a high likelihood of patients with hepatic impairment expected in the intended patient population. There is no PK/safety data available to determine an appropriate dose in patients with moderate or severe hepatic impairment. The proposed study will determine appropriate azacitidine dose(s) in this specific population.	PK/safety study to determine an appropriate dosing regimen of azacitidine for patients with moderate or severe hepatic impairment. Given safety concerns of hepatotoxicity with azacitidine, the study should be designed to enroll patients with moderate hepatic impairment first, and subsequently using PK and safety data in patients with moderate hepatic impairment to guide further evaluation of azacitidine in patients with severe hepatic impairment.

6.2 SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

Oral azacitidine and CC-486 are used interchangeably in this review.

6.2.1 Pharmacology and Clinical Pharmacokinetics

The systemic exposure of oral azacitidine is approximately dose proportional over the dose range of 120 mg to 600 mg once daily (0.4 to 2 times the recommended dosage). Following a single 300 mg dose of oral azacitidine, the geometric mean (coefficient of variation [CV%]) C_{max} and AUC of azacitidine were 145 ng/mL (64%) and 242 ng•h/mL (65%), respectively. No accumulation was observed following CC-486 300 mg once daily.

Absorption

The mean oral bioavailability is approximately 11% relative to subcutaneous administration. The median time to peak plasma concentration of azacitidine is 1 hour.

Effect of Food
A high-fat, high-calorie meal (approximately 800 to 1000 calories, 50% fat) had no effect on

$AUC_{0\text{-}INF}$ and decreased C_{max} by 21% following a single administration of 300 mg CC-486 (300 mg tablet, F9).

Distribution

The mean (CV%) apparent volume of distribution (Vz/F) of azacitidine is 881 L (67%). The *in vitro* serum protein binding of azacitidine is approximately 6% to 12%. The blood-to-plasma ratio is approximately 0.30.

Elimination

The mean (CV%) terminal half-life is approximately 0.5 hours (27%) and the geometric mean apparent clearance (CL/F) is 1240 L/hour (64%).

Metabolism

Azacitidine undergoes spontaneous hydrolysis and deamination mediated by cytidine deaminase.

Excretion

Following oral administration of azacitidine 300 mg QD, <2% of the oral dose was excreted unchanged in the urine.

6.2.2 General Dosing and Therapeutic Individualization

General Dosing

The proposed dosing regimen is 300 mg QD with or without food for the first 14 days of a 28-day cycle.

Therapeutic Individualization

Specific Population

Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment. In the popPK analysis, there was no significant effect of mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin 1 to 1.5 × ULN and any AST, n=34) on azacitidine clearance (CL/F) compared to patients with normal hepatic function (total bilirubin and AST ≤ ULN, n=250). No dose recommendation can be provided for patients with moderate or severe hepatic impairment due to the lack of supportive data.

Renal Impairment

No dose adjustment is recommended for patients with mild to severe renal impairment.
In the prior dedicated PK/safety study in cancer patients with renal dysfunction (study AZA PH US 2007 PK 006), mean azacitidine AUC and C_{max} values increased by approximately 70% or 42% on Day 1, and 40% or 6% on Day 5, respectively, following multiple doses of 75 mg/m^2 SC azacitidine in patients with severe renal impairment (CLcr < 30 mL/min/1.73 m^2, Cockcroft-Gault equation adjusted by BSA) compared with those subjects with normal renal function.

In the present popPK analysis, mild (CLcr ≥ 60 to 90 mL/min calculated by Cockcroft-Gault, n= 117), moderate (CLcr ≥ 30 to 60 mL/min, n=56) or severe renal impairment (CLcr ≥ 20 to 30 mL/min, n=3) reduced typical value of CL/F by 19%, 25% and 38%, respectively, compared to patients with normal renal function (n=110). The reduction in CL/F in patients of varying degree of renal impairment translates to approximately 30 to 60% higher azacitidine exposure which was in agreement with the previous findings from the dedicated PK/safety study.
A trend of higher incidence of neutropenia was noted in patients with renal impairment, consistent with the known E-R relationship for neutropenia. However, there was no clear trend in incidence of grade 3/4 infection or serious infections across renal impairment categories. Dose reduction, interruption, and discontinuation did not increase with severity of RI. The Applicant's proposed risk management of dose modification for Grade 4 neutropenia and Grade 3 neutropenia with fever is acceptable.

Food effect

Consumption of a high-fat, high-calorie meal had no clinically meaningful effect on the oral absorption of the 300 mg F9 tablet. C_{max} was 21% lower (78.9% [68.6, 90.7]) and $AUC_{0\text{-}inf}$ was 9% higher (109% [98.5, 120]) under fed condition compared to fasting subjects.

Gastric Acid Reducing Agents

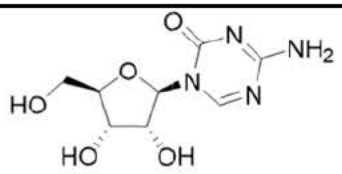
Coadministration of omeprazole (a proton pump inhibitor, 40 mg QD for 4 days) with 300 mg oral azacitidine increased azacitidine AUC_{last} by 18% (118% [101, 137]) and C_{max} by 13% (113% [97.8, 131]) in patients. This magnitude of effect is not expected to be clinically relevant.

Outstanding Issues

The outstanding issue from Clinical Pharmacology perspective will be addressed by the PMR study to assess the effect of moderate and severe hepatic impairment on azacitidine PK/safety.

6.3 COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

Physical and Chemical Properties	
Chemical Structure and Formula	Azacitidine (CC-486)  Molecular formula: C8H12N4O5 (free base) Molecular weight: 244 g/moL
In vitro solubility	Azacitidine is a weak base with pH-dependent solubility. Oral azacitidine (CC-486) is highly soluble in aqueous media across a wide range of pH values. The in vitro solubility of azacitidine is ~26 mg/mL at pH 3 – 7 and increases to ~260 mg/mL at pH 1 at 37°C which exceeds the expected GI concentration at the recommended dose (300 mg/250 mL). Based on its in vitro solubility, CC-486 DP is expected to be completely dissolved in gastric fluid of the stomach and to remain in solution during transition from the stomach into intestine when pH increases from acidic to neutral pH.
Pharmacology	
Mechanism of Action	Azacitidine is a pyrimidine nucleoside analog of cytidine. It exerts antineoplastic effects through multiple mechanisms, including inhibition of DNA methyltransferases. Following active cellular uptake of azacytidine by cell membrane nucleoside transporters, Intracellular azacitidine undergoes sequential phosphorylation resulting in azacytidine triphosphate (5-aza-CTP) which is then incorporated into DNA and RNA. In vitro cellular activities suggested pharmacological activity at the clinical plasma concentrations of azacitidine at the recommended dose (C_{max} of 0.2 to 0.9 μM).
Active Moiety	Azacitidine is the pharmacologically active moiety. There was no report of active metabolites exhibiting substantial cytotoxicity.
QT Prolongation	Per OSE assessment of FAERS, Grade 3/4 QT prolongation related to azacitidine treatment was rare following IV or SC administration of azacitidine with multiple confounding risk factors present, precluding causality assessment. There was no report of ECG QT prolongation finding for oral azacitidine. Azacitidine exposure after 300 mg PO was approximately 75% lower than that after 75 mg/m^2 SC. As such, the Applicant did not conduct concentration-QT analysis.
General Information	
Bioanalysis	Azacitidine (plasma and urine) was quantified using validated LC-MS/MS methods. A summary of the bioanalytical methods and performance is included in the Appendix of this multidisciplinary review.
Healthy Volunteers vs. Patients	CC-486 PK has been characterized in patients with cancer and was not studied in healthy subjects.

Drug exposure following the therapeutic dosing regimen

The geometric means (CV%) of C_{max} and $AUC_{0\text{-}INF}$ on Cycle 1 Day 1, Day 14 and Day 21 following CC-486 300 mg QD administration (Study AZA PH US 2007 CL 005, Part 2, F6 formulation):

Time	PK Parameters	Geometric Mean (CV%)
Cycle 1 Day 1 (n=25)	C_{max} (ng/mL)	124 (68.6%)
	$AUC_{0\text{-}inf}$ (ng•h/mL)	193 (71.9%)
Cycle 1 Day 14 (n=8)	C_{max} (ng/mL)	99 (50.4%)
	$AUC_{0\text{-}inf}$ (ng•h/mL)	166 (52.0%)
Cycle 1 Day 21 (n=6)	C_{max} (ng/mL)	97 (63.3%)
	$AUC_{0\text{-}inf}$ (ng•h/mL)	207 (63.3%)

The geometric mean (CV%) Pharmacokinetic Parameters after single dose of 300 mg CC-486 by Formulation (F8 or F9) in study CC-486-CAGEN-001:

CC-486 Parameter	N	AUC_t (ng•h/mL)	AUC_∞ (ng•h/mL)	C_{max} (ng/mL)	T_{max} (h)[a]	$t_{½}$ (h)	CL/F (L/h)	V_z/F (L)
Formulation 8	30	225.0 (63.7)	228.5 (62.6)	143.0 (53.1)	1.0 (0.48 – 3.0)	0.544 (32.0)	1313 (62.6)	1031 (67.4)
Formulation 9	30	239.1 (65.2)	241.6 (64.5)	145.1 (63.7)	1.0 (0.50 – 2.5)	0.492 (26.9)	1242 (64.5)	881.1 (67.4)

Minimal effective dose or exposure

The proposed (b) (4) dose of CC-486 is 300 mg QD for 14 days out of a 28-day treatment cycle, which was the only dose regimen evaluated in the registration study (CC-486-AML-001). In the Phase 1/2 dose-escalation safety, PK/PD study (AZA-PH-US-2007-CL-005), azacitidine demonstrated concentration-dependent inhibition of global DNA methylation score (GDMS, percentage of highly methylated loci). Seven -day treatment of 300 to 600 mg QD did not result in significant hypomethylation. In comparison, following 300-mg 14-day QD and 21-day QD, GDMSs were reduced on Day 15 (-3.3% and -5.3%, respectively), Day 22 (-3.8% and -6.7%) and end of cycle (-2.4% and -5.0%), respectively. Graphic PK/PD analysis suggested a minimum biologically effective plasma exposure of approximately 100 ng·h/mL (AUC at cycle 1).

Maximal tolerated dose or exposure

Based on the Phase 1/2 dose-escalation study (AZA-PH-US-2007-CL-005), the MTD of 7-day QD dosing schedule was 480 mg.

Dose Proportionality

There was no major deviation from dose-proportionality in azacitidine exposure increase over 120 to 600 mg QD (AZA-PH-US-2007-CL-005, Part 1, F1 or F3 formulations). For an approximately 3.3-fold dose increase from 180 to 600 mg, the Day 7 exposure increased from 126 ng•h/mL to 387 ng•h/mL for AUC.

Accumulation

There was no notable accumulation of azacitidine following 300 mg QD administration due to the short elimination half-life.

Variability

Inter-subject variabilities (CV%) were 69% for C_{max} and 72 % for $AUC_{0\text{-}inf}$ after the 1st dose of azacitidine 300 mg (n=25) (study AZA-PH-US-2007-CL-005).

Absorption

Oral Bioavailability

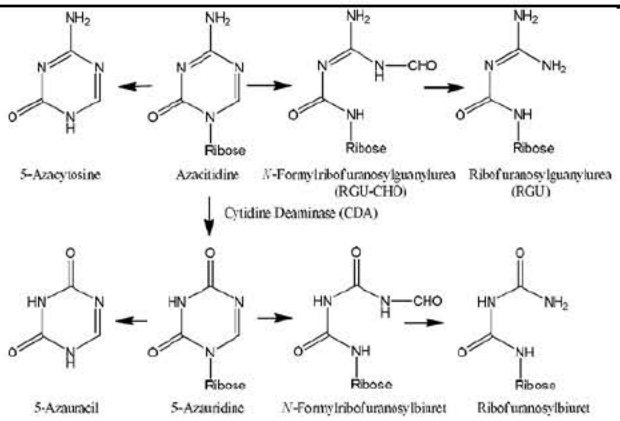
The mean relative oral bioavailability of CC-486 (300 mg) to SC (75 mg/m^2) was 11% (AZA PH US 2007 CL 005, F3).

Bioavailability/Bioequivalence

PK comparability/BE assessment were evaluated between F6 and F8 (AZA-MDS-004, n=16) as well as between F8 and F9 (CC-486-CAGEN-001, n=30). The geometric mean ratios (GMR, 90%CI) are shown below.

Formulation	C_{max}	$AUC_{0\text{-}inf}$
F8 (2X150 mg) to F6 (3x100 mg)	83.3 (67.3, 103)	98.3 (83.8, 115)
F9 (1x300 mg) to F8 (2x150 mg)	102 (90, 115)	106 (95, 118)

<table>
<tr><td>Oral t_{max}</td><td colspan="3">Following administration of a single oral dose of 300 mg CC-486, the median t_{max} ranged from 0.8 hours to 1.5 hours (Study AZA-PH-US-2007-CL-005, Part 2). The median t_{max} was 1 h after oral administration of F9 (CC-486-CAGEN-001)</td></tr>
<tr><td rowspan="3">Food effect

fed/fasted GMR% (90% CI)</td><td colspan="3">In Study CC-486-CAGEN-001, a high-fat, high-calorie meal had no clinically meaningful effect on azacitidine absorption after a single oral dose of 300 mg CC-486 (300 mg tablet, F9) with a modest delay in t_{max} (2 h vs. 1 h) in patients with cancer (n=44 to 56).</td></tr>
<tr><td>C_{max}</td><td>AUC_{last}</td><td>$AUC_{0\text{-}inf}$</td></tr>
<tr><td>78.9 (68.6, 90.7)</td><td>102 (92.8, 112)</td><td>109 (98.5, 120)</td></tr>
<tr><td rowspan="3">Effect of Gastric acid reducing agents with PPI/without PPI GMR% (90% CI)</td><td colspan="3">In Study AZA-MDS-004, coadministration of proton-pump inhibitor omeprazole (40 mg QD, 4-day) had no meaningful effect on C_{max}, AUC_{inf} and the median t_{max} for azacitidine (300 mg, n=14).</td></tr>
<tr><td>C_{max}</td><td colspan="2">$AUC_{0\text{-}inf}$</td></tr>
<tr><td>113 (97.8, 131)</td><td colspan="2">119 (102, 138)</td></tr>
<tr><td>Substrate transporter systems [in vitro]</td><td colspan="3">Azacitidine is not a substrate of P-gp in vitro. Interaction with other drug transporters as substrate has not been determined.</td></tr>
<tr><td colspan="4">Distribution</td></tr>
<tr><td>Volume of Distribution</td><td colspan="3">The geometric mean (CV%) of apparent volume of distribution (V_z/F) was 881 L based on noncompartmental analysis (NCA, CC-486-CAGEN-001). The pop PK estimate of V/F is 889 L (one-compartment model).</td></tr>
<tr><td>Serum Protein Binding</td><td colspan="3">In vitro, 7.42% to 8.79% of azacitidine bound to human serum over concentration of 0.1, 1 and 10 µg/mL</td></tr>
<tr><td>Blood to Plasma Ratio</td><td colspan="3">The mean blood-to-plasma ratio is 30.4-33.2% for azacitidine over 0.1, 1, and 10 µg/mL in vitro.</td></tr>
<tr><td colspan="4">Elimination</td></tr>
<tr><td>Half-life</td><td colspan="3">The mean estimates of terminal $t_{1/2}$ using NCA method ranged from 0.53 to 0.68 hours.</td></tr>
<tr><td>Clearance</td><td colspan="3">The apparent CL/F was 1240 L/h at 300 mg dose by the NCA method (CC-486-CAGEN-001). The Pop PK estimate of CL/F is 1530 L/h.</td></tr>
<tr><td colspan="4">Metabolism</td></tr>
<tr><td>Primary metabolic pathway(s)</td><td colspan="3"> 

Catabolism of azacitidine is via spontaneous hydrolysis and deamination. Spontaneous hydrolysis of azacitidine results in the irreversible formation of ribofuranosylguanylurea (RGU). Deamination, mediated by cytidine deaminase (CDA), is the primary pathway to form 5-azauridine. No human mass balance has been conducted to definitively characterize the in vivo metabolic pathway in human.</td></tr>
</table>

	In vitro, ≤ 17.4% and ≤ 4.3% of azacitidine remained after 45 and 90 minute-incubation in human hepatic S9 fraction, respectively. The biotransformation was shown to be independent of NADPH, indicative of minimal CYP involvement. Exploratory analysis from study AZA PH US 2007 CL 005 did not identify significant correlation between dose-normalized AUC and the six known CDA SNPs.
Inhibitor/Inducer	Clinical DDIs The applicant did not conduct CYP- or drug transporter-based clinical DDI study for azacitidine. In vitro DDIs *CYP isozymes* Azacitidine did not inhibit CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 at concentrations as high as 100 μM; IC_{50} values could not be determined. IC_{50} values were above 100 μM (~30 μg/mL) for CYP1A2 and CYP2E1. Azacitidine concentration as high as 100 μM did not induce CYP1A2, CYP2C19 and CYP3A4 in human hepatocyte incubation based on the functional activity. The effect on mRNA level was not determined. *Drug transporters* Azacitidine (50 μM) had no notable inhibitory effect on P-gp. Less than 25% inhibition at 20 and 200 μM azacitidine for BCRP, OATP1B1, OATP1B3, OAT1, OAT3, or OCT2.
Excretion	
Primary excretion pathways (% dose)	The applicant did not conduct human mass balance study to definitely characterize the excretion pathways for azacytidine and its metabolites. Per Vidaza® label, urinary excretion is the primary route of elimination of azacitidine and its metabolites. Result from Study AZA-PH-US-2007-CL-005 (Part 1) has shown negligible (<2% of the dose) urinary excretion of azacitidine unchanged following oral administration of CC-486.

6.3.2 Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The clinical pharmacology data supported the clinical benefit of CC-486.

The safety, PK/PD and preliminary activities of CC-486 were evaluated in the Phase 1/2 dose-escalation study AZA PH US 2007 CL 005. In Part 1 of the study, the dose range of 120 to 600 mg on the 7-day QD treatment schedule were assessed and MTD was determined to be 480 mg (Table 9). The 7-day QD CC-486 treatment of 300 to 600 mg doses did not result in significant reduction of GDMS (PD marker for DNA hypomethylation) on Day 15 (Table 10). In Part 2, dose regimen/schedules of 300 mg 14-day QD or 21-day QD, and 200 mg 14-day twice daily (BID), or 21-day BID over 28-day cycles were subsequently explored. BID regimens were not well-tolerated due to GI toxicities which resulted in high rates of dose modification. Both QD schedules of 300 mg significantly reduced GDMS over the dosing interval, with 21-day treatment exhibiting greater PD effect. Exploratory analysis suggested a positive E-R trend between azacitidine AUC (cycle 1) and GDMS reduction with minimal biological active concentration at 100 ng•h/mL. The regimen of 300 mg 14-day QD of a 28-day treatment cycle was selected as RP2D based on the totality of data as a maintenance therapy.

Table 9. TEAE Summary During Oral Azacitidine 7- day QD Schedule by Oral Dose Level – Oral Azacitidine Population (AZA PH US 2007 CL 005)

Parameter	Part 1 - 7-day QD[a] Oral Dose Level, n (%)							Overall, n (%)
	120 mg (N = 7)	180 mg (N = 3)	240 mg (N = 3)	300 mg (N = 5)	360 mg (N = 5)	480 mg (N = 15)	600 mg (N = 3)	Total (N = 41)
Subjects With at Least One TEAE	7 (100.0)	2 (66.7)	3 (100.0)	5 (100.0)	5 (100.0)	15 (100.0)	3 (100.0)	40 (97.6)
Subjects With at Least One Serious TEAE	3 (42.9)	2 (66.7)	1 (33.3)	2 (40.0)	3 (60.0)	5 (33.3)	3 (100.0)	19 (46.3)
Subjects With at Least One Grade 3/ 4 TEAE	4 (57.1)	2 (66.7)	1 (33.3)	2 (40.0)	3 (60.0)	10 (66.7)	3 (100.0)	25 (61.0)
Subjects With at Least One TEAE Leading to Death	1 (14.3)	0	0	1 (20.0)	0	1 (6.7)	0	3 (7.3)
Subjects With at Least One TEAE Leading to Dose Discontinuation	0	0	0	0	1 (20.0)	1 (6.7)	1 (33.3)	3 (7.3)
Subjects With at Least One TEAE Leading to Dose Reduction	1 (14.3)	0	1 (33.3)	0	1 (20.0)	3 (20.0)	3 (100.0)	9 (22.0)
Subjects With at Least One TEAE Leading to Dose Interruption	2 (28.6)	1 (33.3)	0	2 (40.0)	2 (40.0)	3 (20.0)	2 (66.7)	12 (29.3)
Subjects With at Least One TEAE Related to Study Drug	3 (42.9)	2 (66.7)	1 (33.3)	3 (60.0)	5 (100.0)	15 (100.0)	3 (100.0)	32 (78.0)
Subjects With at Least One Serious TEAE Related to Study Drug	0	0	0	0	1 (20.0)	1 (6.7)	3 (100.0)	5 (12.2)

Source: Clinical Study Report AZA PH US 2007 CL 005, Table 40.

Table 10. Changes in Global DNA Methylation Score (GDMS) with Subcutaneous Azacitidine or 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

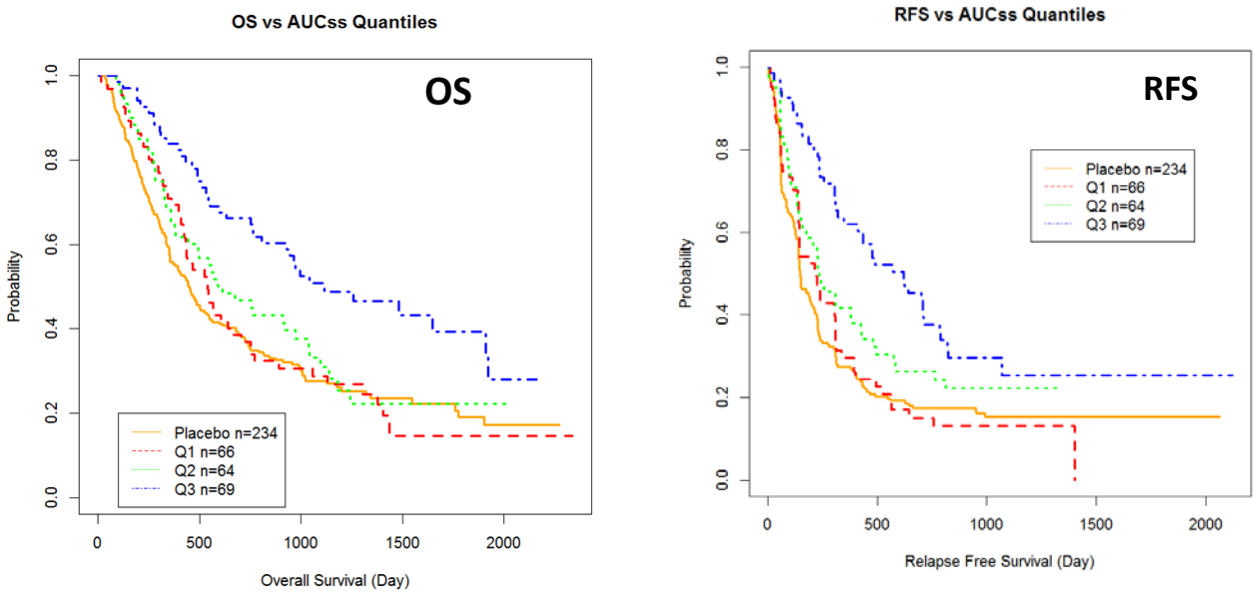
Source: Summary of clinical pharmacology studies, Table 33.

The 300 mg 14-day QD schedule (with the option of extending to 21- days in the event of AML relapse) was further evaluated in the registration study CC-486-AML-001 in AML patients age ≥ 55 years and within 4 months of achieving first CR or CRi with intensive induction chemo-therapy. A total of 472 patients were randomized 1:1 to CC-486 (n=238) or placebo (n=234).

Using data from study CC-486-AML-001, the Applicant's descriptive quantile analysis revealed a positive E-R trend where higher azacitidine exposure (AUC_{ss} estimated by normal dose of 300 mg) correlated with better treatment response in both endpoints of OS and RFS. The findings were further confirmed by the multivariate Cox regression analysis after adjustment of the known baseline risk factors (age, cytogenetic risk and prior consolidation).

Similarly, the FDA descriptive analysis showed an overall consistent visual trend of positive E-R relationship for efficacy. As seen in Figure 7, patients in the Q3 quantile (AUC_{SS} ≥ 238 ng•h/ml) generally exhibited superior response compared to the placebo. In contrast, Kaplan-Meier curves of OS and RFS were largely overlapping between patients of Q1 (AUC_{SS} < 238 ng•h/ml) and placebo with no clear differentiation. FDA reviewer's further analysis on distribution of baseline factors did not identify major imbalance in baseline demographic or disease characteristics across AUC_{ss} Q1 to Q3, and between Q1 vs placebo. See Section 15.4.1 for details.

Figure 7. Kaplan-Meier Curves for OS and RFS by AUC_{ss} Quantile



Source: FDA reviewer's descriptive quantile analysis. AUC_{ss} Tertile 1 < 162 ng·h/mL; Tertile 2 ≥ 162 and < 238 ng·h/mL, Tertile 3 ≥ 238 ng·h/mL

Taken together, the available data suggest a positive trend in the exposure-efficacy relationship based on the data from the proposed regimen of 300 mg QD.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The proposed dose regimen of 300 mg QD is appropriate for the intended AML population. The efficacy consideration is summarized as above. The safety aspect and benefit/risk are discussed below.

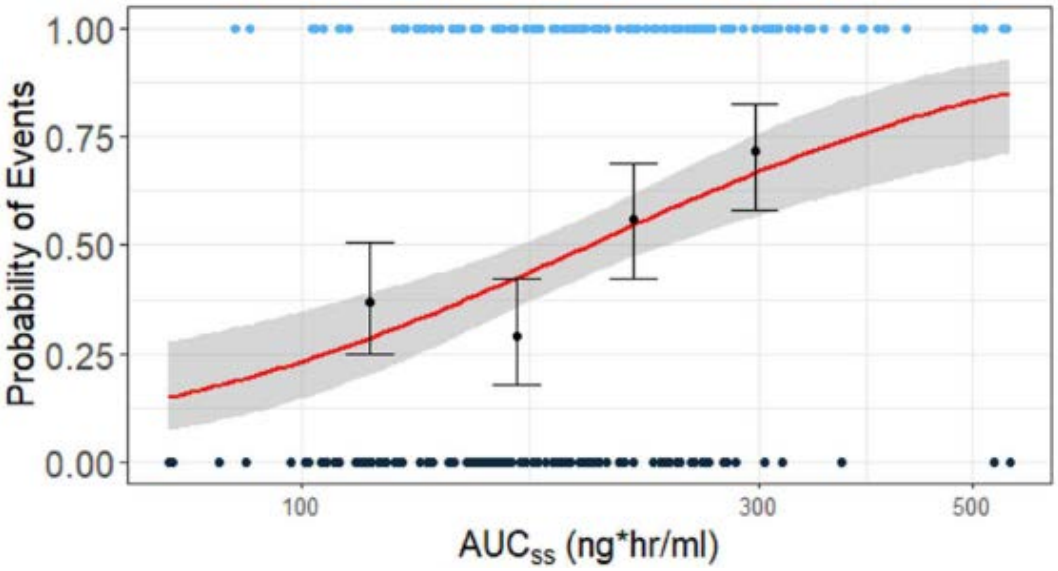
In Part 1 of Phase 1/2, dose escalation study AZA PH US 2007 CL 005, the MTD on the 7-day QD treatment schedule was determined to be 480 mg, two of three subjects in 600 mg cohort experienced a DLT of Grade 3 or Grade 4 diarrhea, assessed as drug-related by investigators.

The safety profiles of CC-486 at the RP2D dose of 300 mg QD for 14-day was further assessed in the study CC-486-AML-001. The most common adverse reactions of any grade with CC-486 treatment were GI toxicities, including nausea, vomiting, diarrhea and constipation, the majority of which were of grade 1 or 2 severity. The most common adverse reactions of grade ≥ 3 were hematological toxicities, including neutropenia which occurred more frequently than that in the placebo arm (41% vs 22%). The most common SAE was febrile neutropenia (CC-486: 6.8%; placebo: 3.9%). Treatment discontinuation due to an AE occurred in 7% of patients receiving CC-486; the common (> 1%) adverse reactions which resulted in permanent discontinuation included nausea, diarrhea, and vomiting. Dose reductions due to an adverse reaction occurred in 14% of patients receiving CC-486; the common (>1%) adverse reactions requiring dosage reduction included neutropenia, diarrhea, thrombocytopenia, and nausea.

Treatment interruptions due to an adverse reaction occurred in 36% of patients receiving CC-486; the common (>5%) adverse reactions leading to treatment interruption included neutropenia, thrombocytopenia and nausea. Neutropenia was the most common AE requiring dose interruption (20% vs. 6%) or dose reduction (5.5% vs. 0.4%) in both arms.

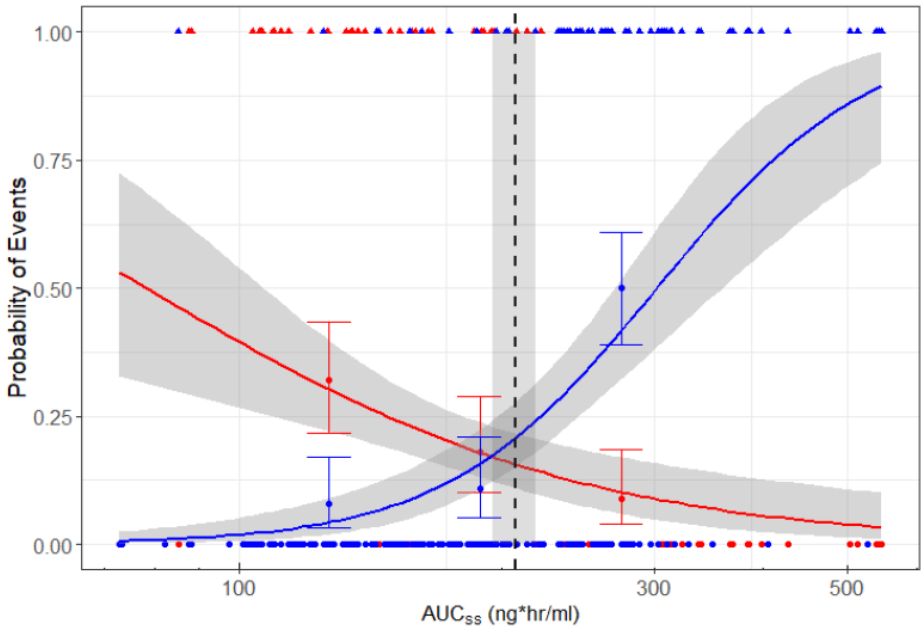
Using safety data from study CC-486-AML-001, the applicant conducted exploratory exposure-safety analyses for select hematological and GI toxicities. Descriptive and univariate logistic regression analyses identified positive E-R relationship for Grade ≥ 3 neutropenia (Figure 8) and diarrhea of any grade (1st two cycles, not shown). Moreover, as seen in Figure 9, higher AUC_{SS} was associated with a lower probability of schedule extension (14 to 21 days) due to AML relapse and higher probability of dose reduction due to AEs. The median exposure at the proposed dose regimen of 300 QD demonstrated similar probability of dose modifications between treatment extension (efficacy) and toxicities (Figure 9).

Figure 8. Logistic Model of Probability of Grade ≥ 3 Neutropenia



Source: Module 2.7.2 Summary of clinical pharmacology studies, Figure 6

Figure 9. Logistic Model of Probability of Dose Modifications Due to Relapse or AEs



AUC_{ss} = area under the concentration-time curve at steady state.
The red line is the model predicted probability of dose modification due to relapse and the blue line is the model predicted probability of dose modification due to AE, the gray shaded area is the 95% confidence interval from logistic regression. The round symbols with error bars represent the observed data with 95% confidence interval. The blue and red round symbols are subjects with no dose reduction or schedule extension, respectively. The blue and red triangle symbols are subjects with observed dose reduction or schedule extension, respectively. The black dashed line is the estimated mean AUC_{ss} and the gray shaded area is the 95% confidence interval.

Source: Module 2.7.2 Summary of clinical pharmacology studies, Figure 10.

In summary, the available safety data and exposure-safety analysis demonstrated the association of increasing azacitidine exposure with higher incidence of Grade 3/4 neutropenia and consequently the higher potential of dose reduction due to AEs. Taking the positive E-R relationship for efficacy into consideration, the proposed dosing regimen of 300 mg QD provides a balanced benefit/risk profile and is considered adequate for the general patient population from a clinical pharmacology standpoint.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Based on the pop PK analysis (CC-486-MPK-001, pooled studies AZA-MDS-004, CC-486-CAGEN-001 and CC-486-AML-001), age (46 to 93 years, median=68.5), sex (F:46%, M:54%), body weight (39.3 to 129 kg, median=72.9), and organ dysfunction (mild hepatic impairment [total bilirubin > 1 to 1.5 x ULN or AST > ULN] or renal impairment [19.5 to 90 mL/min]) had no clinically meaningful effect on the systemic exposure of CC-486; therefore, no dose adjustment is recommended with respect to these intrinsic factors. The effect of race could not be determined given that the population was generally homogenous (White [92%], Asian [2.3%]).

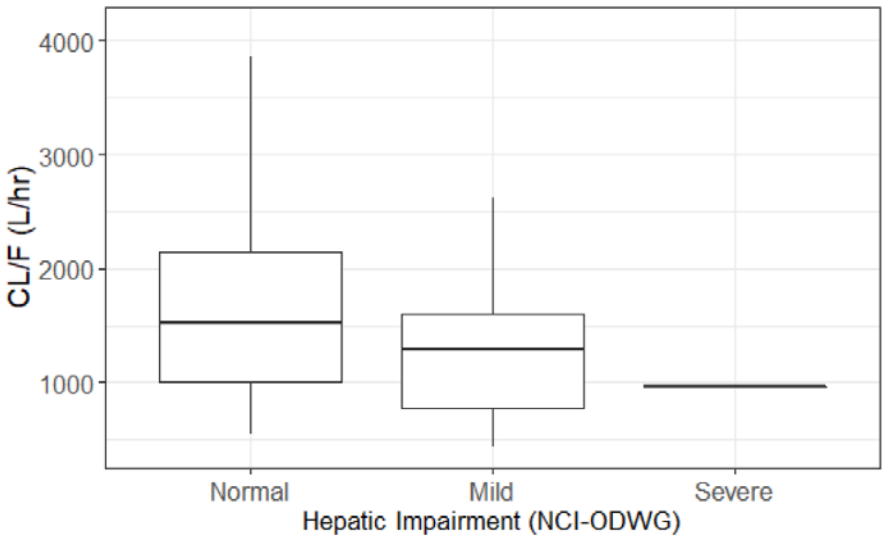
Hepatic impairment

Azacitidine is primarily eliminated via spontaneous hydrolysis and deamination by CDA. Since no human mass balance study was conducted, the relative contribution of each metabolic pathway has not been fully characterized. CDA was reported to have widespread tissue expression and it is highly expressed in leukocytes and liver. In vitro study showed poor stability of azacitidine in human hepatic S9 incubation, indicative of considerable hepatic metabolism.

Per the Vidaza® label, patients with pre-existing severe hepatic impairment are subjected to a higher risk of hepatoxicity following a SC or an IV dose of 75 mg/m^2. Using NCI-ODWG criteria for hepatic impairment classification, analyses of Vidaza study 9221 and postmarketing data revealed that there was no clinical experience in patients with severe hepatic impairment and safety data were also limited for patients with moderate hepatic impairment. In the present development program of oral azacitidine (CC-486), patients with moderate to severe hepatic impairment (total bilirubin >1.5x ULN) were excluded from the clinical studies.

The pop PK analysis included patients with normal liver function (n= 250) and patients with mild hepatic impairment by NCI ODWG criteria (n= 34) at baseline, and the results indicated that mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin 1 to 1.5 × ULN and any AST) had no significant effect on azacitidine CL/F. The median CL/F for normal hepatic function and mild hepatic impairment was 1520 and 1290 L, respectively (Figure 10). Therefore, no dose adjustment is recommended for patients with mild hepatic impairment.

Figure 10. Azacitdine CL/F by Hepatic Impairment Categories



Source: CELGENE RESPONSE TO FDA REQUEST FOR INFORMATION DATED 02 JUNE 2020. N=1 in severe hepatic impairment group.

As the effects of moderate (total bilirubin > 1.5 to 3x ULN) and severe (total bilirubin > 3 x ULN) hepatic impairment on the exposure of azacitidine and safety have not been studied, and hepatic metabolism is the one of major elimination pathway for azacitidine, the labeling recommendation is to avoid administration of CC-486 in patients with severe hepatic impairment. For patients with pre-existing moderate hepatic impairment, consider the risks and potential benefits before initiating treatment. A dedicated hepatic impairment study will be required as a PMR.

Renal impairment

Publication of ADME studies with labeled azacitidine (referenced in Module 2.7.2) indicated that renal excretion is the primary elimination pathway for azacitidine and its metabolites. Following intravenous administration of radioactive azacitidine, the cumulative urinary excretion was 85% of the radioactive dose (Vidaza label). The renal elimination of azacitidine as parent is negligible, with < 2% of dose excreted unchanged in the urine (studies AZA PH US 2007 PK 006 [PMR study under NDA 050794] and AZA PH US 2007 CL 005).

In the PK/safety study in cancer patients with impaired renal function (AZA PH US 2007 PK 006), azacitidine exposure (AUC) increased by ~ 70% after a single dose and 41% at steady-state in patients with severe renal impairment compared to patients with normal renal function following multiple SC dose of 75 mg/m^2 QD (Table 11). There was no major effect of severe renal impairment on the safety of azacitidine. According to the clinical pharmacology review (Reference ID: 3400640), when AUC_{inf} at 75 mg/m^2 in patients with severe renal impairment and AUC_{inf} at 100 mg/m^2 in patients with normal renal function are compared, the individual values were similar. Given that a dose escalation to 100 mg/m^2 may be considered if no beneficial effect has been seen after 2 cycles of 75 mg/m^2 and if no toxicity (other than nausea

and vomiting) has occurred, a 70% higher exposure in patients with severe renal impairment does not require dose adjustment. However, patients with severe renal impairment should not be dose-escalated to 100 mg/m^2 per the label.

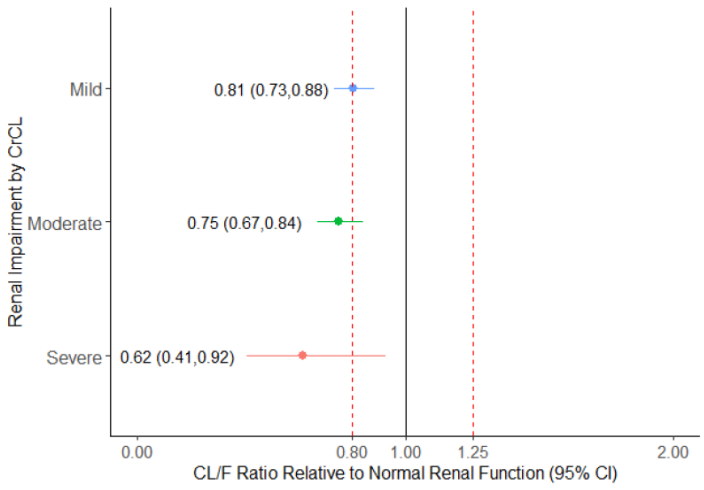
Table 11. Azacitidine Exposure in Patients with or without Renal Dysfunction (AZA PH US 2007 PK 006)

PK Parameter	Visit	Geometric Mean		Ratio (%) of Geometric Means[a]	90% CI of Ratio of Geometric Means
		Cohort 3 (n = 6)	Cohort 5 (n = 6)		
AUC_{0-inf} (ng*hr/mL)	Day 1	946.22	1573.82	166.3	(108.6, 254.6)
	Day 5	857.64	1210.92	141.2	(92.2, 216.2)
AUC_{0-t} (ng*hr/mL)	Day 1	920.76	1558.72	169.3	(109.2, 262.5)
	Day 5	841.62	1181.83	140.4	(90.6, 217.7)
C_{max} (ng/mL)	Day 1	745.50	1056.66	141.7	(73.2, 274.6)
	Day 5	632.56	668.11	105.6	(54.5, 204.6)

Source: study AZA PH US 2007 PK 006 CSR, Table 15. Cohort 5 patients with severe renal impairment and cohort 3 normal renal function.

Consistently, the current pooled popPK analysis showed that subjects with mild (CL_{cr} 60 to 90 mL/min, n=117), moderate (CL_{cr} 30 to 60 mL/min, n=56) or severe (CL_{cr} 15 to 30 mL/min, n=3) renal impairment had approximately 19%, 25% and 38% slower clearance, respectively (Figure 11).

Figure 11. Forest Plot of CLcr on CL/F in Final pop PK Model



Normal (N=110): CLcr > 90 mL/min; Mild (N=117): 60 ≤ CLcr < 90 mL/min; Moderate (N=56): 30 ≤ CLcr < 60 mL/min; Severe (N=3): 15 ≤ CLcr < 30 mL/min.

Source: Clinical PK/PD Report CC-486-MPK-001, Figure 5.

In the safety subgroup analysis for study CC-486-AML-001 by renal function group (mild to moderate), a trend of increased neutropenia incidence was noted in the patients with renal dysfunction (Table 12 and Table 13), which was in accordance with the E-R relationship for

neutropenia. However, no appreciable difference in the incidence of Grade 3/4 infection or serious infections was noted between patients with normal renal function and those with mild to moderate renal impairment. Dose reduction, interruption, and discontinuation did not increase with severity of RI. In the CC-486 treatment group, the overall incidence of TEAEs leading to dose reduction, dose interruption, and both dose interruption and dose reduction were highest in subjects with mild renal impairment (20.0%, 44.8%, 13.3%, respectively) compared to normal renal function group (9.7%, 43.0% and 7.5%) and moderate renal function group (18.4%, 39.5% and 7.9%). As such, no dose adjustment for renal impairment is recommended and the risk of neutropenia may be managed via dose modification for AEs.

Table 12. Select TEAEs Reported for ≥ 10% in the CC-486 Treatment Group with Any Baseline Renal Function Status by SOC and PT – Safety Population (Excluding AML Relapse)

System Organ Class Preferred Term[a]	Renal Function[b] CC-486 (N = 236)				Renal Function[b] Placebo (N = 232)			
	Normal (N = 93) n (%)	Mild (N = 105) n (%)	Moderate (N = 38) n (%)	Total (N = 236) n (%)	Normal (N = 97) n (%)	Mild (N = 99) n (%)	Moderate (N = 36) n (%)	Total (N = 232) n (%)
Abdominal pain upper	8 (8.6)	11 (10.5)	2 (5.3)	21 (8.9)	5 (5.2)	5 (5.1)	2 (5.6)	12 (5.2)
Blood and lymphatic system disorders	**56 (60.2)**	**69 (65.7)**	**30 (78.9)**	**155 (65.7)**	**46 (47.4)**	**50 (50.5)**	**13 (36.1)**	**109 (47.0)**
Neutropenia	32 (34.4)	54 (51.4)	19 (50.0)	105 (44.5)	24 (24.7)	29 (29.3)	7 (19.4)	60 (25.9)
Thrombocytopenia	31 (33.3)	34 (32.4)	14 (36.8)	79 (33.5)	26 (26.8)	29 (29.3)	8 (22.2)	63 (27.2)
Anaemia	16 (17.2)	25 (23.8)	7 (18.4)	48 (20.3)	21 (21.6)	16 (16.2)	4 (11.1)	41 (17.7)
Febrile neutropenia	10 (10.8)	15 (14.3)	3 (7.9)	28 (11.9)	7 (7.2)	11 (11.1)	0	18 (7.8)
Leukopenia	9 (9.7)	9 (8.6)	7 (18.4)	25 (10.6)	11 (11.3)	7 (7.1)	1 (2.8)	19 (8.2)

Source: Celgene Response to FDA Information Request Dated 21 Apr 2020, Table 5.

Table 13. Select Grade 3 or 4 TEAEs Reported for ≥ 10% in the CC-486 Treatment Group with Any Baseline Renal Function Status by SOC and PT – Safety Population (Excluding AML Relapse)

System Organ Class Preferred Term [a]	Renal Function [b] CC-486 (N = 236)				Renal Function [b] Placebo (N = 232)			
	Normal (N = 93) n (%)	Mild (N = 105) n (%)	Moderate (N = 38) n (%)	Total (N = 236) n (%)	Normal (N = 97) n (%)	Mild (N = 99) n (%)	Moderate (N = 36) n (%)	Total (N = 232) n (%)
Subjects with at least one grade 3/4 TEAE	58 (62.4)	82 (78.1)	29 (76.3)	169 (71.6)	64 (66.0)	64 (64.6)	18 (50.0)	146 (62.9)
Blood and lymphatic system disorders	**42 (45.2)**	**66 (62.9)**	**23 (60.5)**	**131 (55.5)**	**39 (40.2)**	**45 (45.5)**	**12 (33.3)**	**96 (41.4)**
Neutropenia	29 (31.2)	50 (47.6)	18 (47.4)	97 (41.1)	23 (23.7)	26 (26.3)	6 (16.7)	55 (23.7)
Thrombocytopenia	19 (20.4)	25 (23.8)	9 (23.7)	53 (22.5)	19 (19.6)	24 (24.2)	7 (19.4)	50 (21.6)
Anaemia	13 (14.0)	16 (15.2)	4 (10.5)	33 (14.0)	14 (14.4)	13 (13.1)	3 (8.3)	30 (12.9)
Febrile neutropenia	10 (10.8)	15 (14.3)	2 (5.3)	27 (11.4)	7 (7.2)	11 (11.1)	0	18 (7.8)
Leukopenia	6 (6.5)	6 (5.7)	6 (15.8)	18 (7.6)	10 (10.3)	3 (3.0)	1 (2.8)	14 (6.0)

Source: Celgene Response to FDA Information Request Dated 21 Apr 2020, Table 6.

Body Weight

Reviewer's sensitivity analysis using the applicant's final population PK model revealed that body weight (39.3 to 129 kg, median=72.9) has significant effect on azacitidine clearance, with higher exposure expected in subjects with lower body weight.

Based on subgroup analysis on efficacy and safety, the separations in OS and RFS between azacitidine and placebo appeared to be smaller in patients with higher body weight (≥ 72.9 kg), than that in patients with lower body weight (< 72.9 kg). On the other hand, patients with low baseline body weight appeared to have higher incidence of treatment emergent Grade 3 or 4 neutropenia, and higher probability to reduce azacitidine dose. However, the effect is not considered clinically significant to warrant dose adjustment. Refer to Section 15.4.1 for details about FDA reviewer's analysis.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Food-Drug Interaction

CC-486 can be administered with or without food.

The effect of a high-fat, high-calorie meal on systemic exposure of CC-486 was assessed in patients with cancer receiving a single dose of 300 mg CC-486 (300 mg tablet, F9 formulation) under either fed or fasted condition (study CC-486-CAGEN-001).

As shown in Table 14, mean azacitidine exposure only slightly changed following a single administration of 300 mg CC-486 under fed condition relative to fasting with modestly delayed median t_{max} (2 h vs. 1 h). The food effect is not clinically relevant, thereby supporting administration of CC-486 irrespective of food intake.

Table 14. Effect of Food on The Absorption of Azacitidine with Tablet Formulation (300 mg strength, F9)

Parameter	Treatment	N	Geometric Mean	Ratio (%) of Geometric Means (Fed/Fasted)	90% CI of Ratio (%) of Geometric Means (Fed/Fasted)	Intra-subject CV%
AUC_t (ng*h/mL)	Fasted	56	227.8	101.74	(92.831, 111.507)	29.0
	Fed	55	231.8			
AUC_∞ ((ng*h/mL)	Fasted	54	237.5	108.93	(98.484, 120.474)	28.3
	Fed	44	258.7			
C_{max} (ng/mL)	Fasted	56	133.0	78.86	(68.579, 90.678)	45.5
	Fed	55	104.9			

Source: Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 23

Drug-Drug Interactions (DDI)

Effects of other drugs on azacitidine

Gastric Acid-reducing agent

Dose adjustment is not recommended for CC-486 when coadministered with proton pump inhibitors (PPI).

Azacitidine is a weak base with pH-dependent solubility in vitro. CC-486 is highly soluble in aqueous media over a wide range of pH values, ranging from ~26 mg/mL at pH 3 – 7 to ~260 mg/mL at pH 1. The *in vitro* solubility over the GI pH range far exceeds the expected drug concentration at the recommended dose of 300 mg (300 mg/250 mL ~ 1.2 mg/mL).

Consistently, administration of a proton pump inhibitor omeprazole (40 mg QD for 4 days) had no clinically relevant effect on a single dose CC-486 exposure as shown in Table 15. The median t_{max}s were comparable in the presence or absence of omeprazole (1.49 h vs. 1.43 h).

Table 15. Effect of omeprazole (40 mg QD) on exposure of azacitidine (300 mg PO)

PK Parameter	Treatment Received	N	Geometric Mean	Ratio (%) of Geometric Means	90% CI of Ratio of Geometric Means	Intra-subject CV%
AUC_t (ng*h/mL)	Azacitidine + omeprazole	14	267.3	117.7	(100.9, 137.4)	23.4
	Azacitidine	14	227.0			
AUC_∞ (ng*h/mL)	Azacitidine + omeprazole	14	270.7	118.6	(101.9, 138.1)	23.0
	Azacitidine	14	228.2			
C_{max} (ng/mL)	Azacitidine + omeprazole	14	153.3	113.2	(97.8, 130.9)	22.0
	Azacitidine	14	135.5			

Source: AZA-MDS-004 CSR, Table 17

Effects of azacitidine on other drugs

Based on the in vitro data, CYP- and drug transporter-mediated DDI risk with CC-486 as a perpetrator is low.

7 SOURCES OF CLINICAL DATA AND REVIEW STRATEGY

7.1 TABLE OF CLINICAL STUDIES

Table 16. Clinical Trials in NDA 214120

Trial Identifier (NCT #)	Trial Design	Population	Primary Endpoint
Pivotal Trial			
CC-486-AML-001 (QUAZAR)	Randomized, open-label, Phase 3 trial of oral azacitidine vs placebo Oral aza: 300 mg PO QD x 14/28 days Placebo: PO QD x 14/28 days	Adults with AML in first CR/CRi after intensive induction therapy with or without consolidation N = 469 randomized Oral aza: 236 Placebo: 233	OS
Studies to Evaluate Drug Activity and Safety			
AZA-MDS-004	Single-arm PK study Oral aza: 300 mg QD x 21/28 days	Adults with R/R MDS, CMML, or AML N = 32 AML n = 9	PK
AZA-PH-US-2008-CL-008	Single-arm PK study Part 1: SC aza 75 mg/m^2 Day 1 and 15 in Cycle 1 + oral aza on Days 3 and 5; then QD x 7/28 Part 2: 600 mg x 7/28	Adults with R/R MDS, CMML, AML, MM, or lymphoma N = 31 AML n = 4	PK
AZA-PH-US-2007-CL-005	Single-arm dose-escalation study Part 1: SC aza 75 mg/m^2 QD x 7 in Cycle 1, Oral aza starting dose: 120 mg PO QD x 7 Part 2: 300 mg QD x 14/28, 200 mg BID x 14/28, 300 mg QD x 21/28, 200 mg BID 21/28	Adults with R/R MDS, CMML, or AML N = 131 AML n = 23	MTD
Additional Studies to Evaluate Safety			
AZA-MDS-003	Randomized, placebo-controlled trial Oral aza: 300 mg x 21/28 days	Adults with lower-risk MDS N = 216 Oral aza: 107 Placebo: 109	OS
CC-486-AML-002	Single-arm dose-finding study Oral aza: 150, 200, or 300 mg QD x 7 or 14/28	Adults with AML or MDS postHSCT N = 30 AML N = 26	MTD
AZA-MDS-005	Single-arm PK study Oral aza: 200 mg or 400 mg Day 1, 300 mg QD D4-24 of 31-day cycle	Adults with MDS N = 5	PK
CC-486-MDS-001	Single-arm dose-finding study Oral aza: 100, 200, or 400 mg for 14 or 21 days of a 28-day cycle	Japanese adults with hematologic neoplasms N = 2	MTD
AZA-ST-001	Single-arm dose-escalation and dose expansion of oral azacitidine as a monotherapy and in combination with carboplatin or nabpaclitaxel Oral aza: 200 mg or 300 mg in varied schedules	Adults with R/R solid tumors N = 41	MTD
CC-486-NPC-001	Single-arm trial Oral aza: 300 mg x 14/21 days	Adults with R/R nasopharyngeal carcinoma N = 36	ORR

Source: FDA analysis

7.2 REVIEW STRATEGY

The Applicant submitted information from 15 clinical trials of oral azacitidine alone or in combination with other agents. Only the pivotal trial CC-486-AML-001 was relevant to determining efficacy in the intended population. Studies AZA-MDS-004, AZA-PH-US-2008-CL-008, and AZA-PH-US-2007-CL-005 were evaluated for data supporting the biological activity of the oral formulation in treatment of AML. Table 1 lists the 10 trials included in the integrated safety database submitted by the Applicant; these 10 trials were included in the clinical review of safety in this NDA.

The key materials used for the review of efficacy and safety included:

- NDA datasets, clinical study reports, case report forms, and responses to IRs
- Relevant published literature
- Relevant information in the public domain

Table 17 lists the submission and amendments reviewed.

Table 17. sBLA Submission and Amendments

eCTD SDN	Received	Category	Subcategory
0001	3/3/20	Original	NDA Original Application
0004	4/13/20	Clinical IR	Response to Information Request
0007	5/5/20	Statistical IR	Response to Information Request
0018	6/24/20	Clinical and CDRH IR	Response to Information Request
0021	7/16/20	Clinical IR	Response to Information Request
0025	7/31/20	Labeling	Package Insert Draft – response data tables included

All major efficacy and safety analyses were reproduced or audited. Statistical analyses by the reviewers were performed using R and SAS/JMP 13.1.0 (SAS Institute, Inc., Cary, NC). Safety analyses were performed using MedDRA-Based Adverse Event Diagnostics (MAED) 1.8 (Enterprise Performance and Lifecycle System Design).

8 STATISTICAL AND CLINICAL EVALUATION

8.1 REVIEW OF RELEVANT INDIVIDUAL TRIALS USED TO SUPPORT EFFICACY

8.1.1. Study CC-486-AML-001 (QUAZAR)

Trial Design

Study CC-486-AML-001 (QUAZAR) is an international, multicenter, placebo-controlled, Phase 3 study with a double-blinded, randomized, parallel-group design to compare CC-486 plus best supportive care (BSC) versus BSC as maintenance therapy in subjects with acute myeloid leukemia (AML) in first complete remission (CR) or complete remission with incomplete blood count recovery (CRi).

Objectives

Primary Objective:

- To evaluate whether maintenance therapy with CC-486 improved overall survival (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.

Secondary Objectives:

- To determine relapse free survival (RFS);
- To determine safety, tolerability;
- To determine the effect of CC-486 compared with placebo on health-related quality-of-life (HRQoL) and healthcare resource utilization.

Exploratory Objectives:

- To determine plasma concentration of azacitidine and explore exposure-response relationships of efficacy and safety endpoints;
- To determine complete cytogenetic remission (CRc) rate;
- To evaluate molecular and/or cellular markers in the bone marrow post-induction and during maintenance therapy that may be predictive of clinical outcomes with therapy (placebo or CC-486), including OS and RFS, following CR/CRi;
- To evaluate exploratory HRQoL measures.

Study Population (Key Eligibility Criteria)

- Adults ≥ 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 (MDS) or chronic myelomonocytic leukemia (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;
- ECOG performance status of 0-3;
- Adequate bone marrow function:
  - ANC ≥ 0.5 x 10^9/L;
  - Platelet count ≥ 20 x 10^9/L.
- Adequate organ function:
  - Serum bilirubin ≤ 1.5 x the upper limit of normal (ULN);
  - Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN;
  - Serum creatinine ≤ 2.5 x ULN;
- Exclude subjects who had prior bone marrow or stem cell transplantation;
- Exclude subjects who achieved CR/CRi following therapy with hypomethylating agents;
- Exclude subjects who received therapy with hypomethylating agents for MDS and subsequently developed AML within 4 months of discontinuing the therapy with HMAs;
- Exclude subjects who had proven central nervous system leukemia;
- Exclude subjects who were a candidate for allogeneic bone marrow or stem cell transplant at screening;
- Exclude subjects who used other experimental drug or therapy within 28 days prior to Day 1 of Cycle 1;

Study Design and Treatment

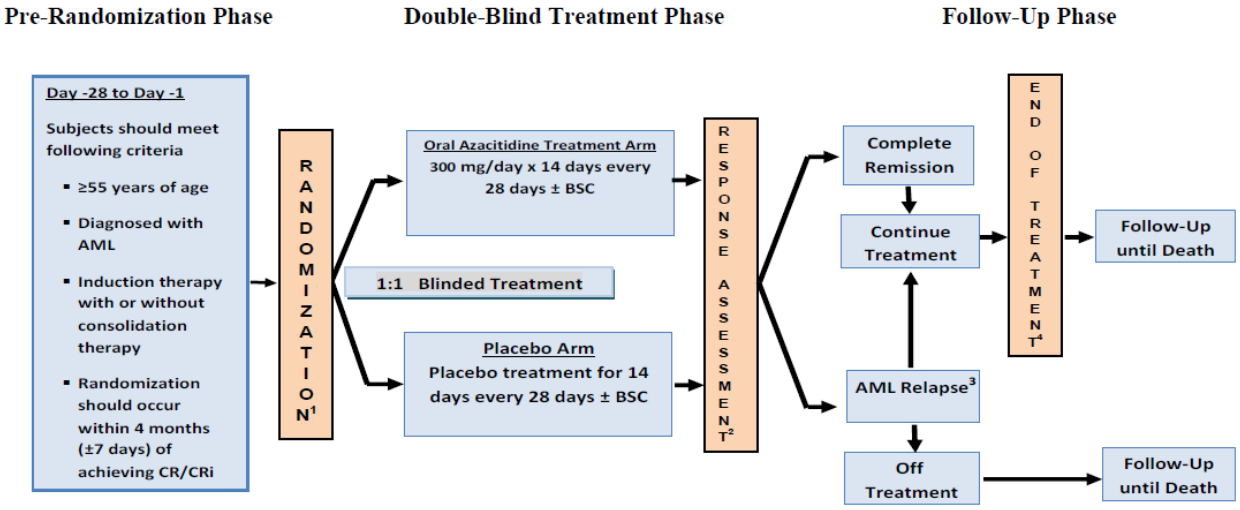
The study consisted of 3 phases: Pre-randomization Phase (Screening Phase), Treatment Phase, and Follow-up Phase. The study protocol was amended to include an Extension Phase (EP), which allowed subjects receiving CC-486 and demonstrating clinical benefit as assessed by the Investigator to continue to receive CC-486 after unblinding by the Applicant until they met the criteria for study discontinuation or until CC-486 became commercially available and reimbursed.

Patients were randomized at a 1:1 ratio and stratified by age at time of induction therapy (55 to 64 years versus ≥ 65 years), prior history of MDS or CMML (yes versus no), cytogenetic risk category at time of induction therapy (intermediate-risk versus poor-risk) and received consolidation therapy following induction (yes versus no).

The starting dose for subjects was 300 mg CC-486 (or placebo) once daily (QD) for the first 14 days of each 28-day treatment cycle. In order to proceed to the next cycle, subjects were required to continue to meet renal and hepatic entry criteria. Subjects were to continue to receive study treatment for at least 2 cycles before being assessed for disease relapse. BSC in both treatment arms included, but was not limited to, red blood cell and platelet transfusions, use of an erythropoiesis stimulating agent, antibiotic, antiviral, and antifungal therapy, nutritional support, and granulocyte colony-stimulating factor for subjects experiencing neutropenic infections.

Crossover between the treatment groups was not allowed so as not to compromise the assessment of the OS endpoint.

Figure 12. Study Design



Source: Figure 1 in the Applicant's Clinical Study Report on Page 33.

Safety Assessments

Figure 13. CC-486-AML-001 – Schedule of Safety Assessments

Procedure	Pre-Randomization Phase	Double-blind Treatment Phase							Post-Treatment Follow-up Phase	
			Cycle 1		Cycle 2		Cycle 3 and Beyond			
	Visit 1/Screen (Day -28 to -1)[1]	Random-ization	Day 1[1]	Day 8, 15, 22 (± 3 days)	Day 1 (± 3 days)	Day 8, 15, 22 (± 3 days)	Day 1 (± 3 days)	Day 15[30] (± 3 days)	Treat-ment Discontin-uation	Follow -up[28]
Randomization	--	×	--	--	--	--	--	--	--	--
Safety Assessments										
Adverse Events	After signing ICD and until 28 days after the last IP dose or until the last study visit, whichever period is longer									
Second Primary Malignancy[9]	After signing ICD and throughout the duration of the study including post treatment follow-up period									
Physical Examination	×	--	×	--	×	--	×	--	×	--
Vital Signs and Body Weight[10]	×	--	×	--	×	--	×	--	×	--
Hematology[11]	×	--	×	×	×	×	×	×	×	--
Serum Ferritin[12]	×	--	×[12]	--	--	--	--	--	×	--
Unstained Peripheral Blood Smear[13]	×	--	×	×	×	×	×	×	×	--
Serum Chemistry[14]	×	--	×	--	×	--	×	--	×	--
Pregnancy Testing (FCBP only)[15]	×	--	×	--	×	--	×	--	×	--
Concomitant Medications, Therapy & Procedures[16]	--	--	×	×	×	×	×	×	×	--

Source: Applicant-submitted Protocol CC-486-AML-001 Table 1

Statistical Analysis Plan

Endpoints

- Primary endpoint:
  - OS, defined as time from randomization to death from any cause, assessed daily.

- Secondary Endpoints:
  - RFS, derived programmatically based on IWG AML response criteria using clinical data, defined as the time from randomization to the earliest date of death or documented relapse, which was defined as any of the following:
    - ≥ 5% bone marrow blasts from the central pathology report;
    - the appearance of > 0% blasts in the peripheral blood with a later bone marrow confirmation (bone marrow blasts ≥ 5%) within 100 days; or
    - at least 2 peripheral blasts ≥ 5% within 30 days.;
  - Time to relapse from CR/CRi;
  - Time to discontinuation from treatment;
  - Safety/tolerability (type, frequency, severity, and relationship of adverse events to study treatments; physical examination findings, vital signs measurements; clinical laboratory evaluations, and concomitant medication/therapy); Patient-reported outcomes (PROs) utilizing the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale and the European Quality of Life-5 dimensions-3 levels (EQ-5D-3L) health utility index;
  - Measures of healthcare resource utilization.

- Exploratory Endpoints:
  - Correlative analyses to assess the relationships between azacitidine exposure and pharmacodynamic (e.g., safety, efficacy) and other exploratory (e.g., biomarker) endpoints;
  - Flow cytometric analysis of hematopoietic cell immunophenotypes;
  - Analysis of genetic alterations, including gene sequencing for recurrent gene aberrations in AML; and
  - HRQoL assessment.

Statistical Reviewer's comment: FDA defines RFS in AML as time from CR to relapse or death. Sensitivity analyses are presented below for this endpoint, termed "RFS per FDA definition". In addition, FDA defined CR as below. CR/CRi status at baseline were adjudicated by clinical team and used for all the reviewer's analysis unless other specified. Due to no lab data available for adjudication of firstly achieved CR/CRi status after induction which occurred up to 4 months prior to randomization, response after induction were provided by the applicant and were used for all the reviewer's analysis.

Clinical Reviewer's comment: FDA adjudicated baseline status as follows –

- ***CR: bone marrow blasts < 5% with neutrophils > 1 Gi/L and platelets > 100 Gi/L on a single***

CBC within ± 14 days of the marrow

- ***CRi: bone marrow blasts < 5% and either neutrophils < 1 Gi/L or platelets < 100 Gi/L with full recovery of the other cell line on a single CBC within ± 14 days of the marrow***

Sample Size

Assuming a median OS of 16 months in the control arm and 22.9 months in CC-486 treated arm, a total of 330 deaths were needed to detect a HR of 0.70 with 90% power at a one-sided alpha level of 0.025. A sequential gate-keeping procedure was specified to control for multiplicity arising from testing multiple endpoints. OS would be tested first at two-sided 0.05 significant level, and RFS would only be tested if the null hypothesis associated with OS was rejected. One interim analysis was planned for futility at approximately 99 deaths (30% information). The study design employed Gamma (-10) as beta-spending function.

Analysis Population

- Intent-to-Treat (ITT) Population: it included all randomized subjects. It was used for the analysis of primary and secondary efficacy endpoints, with treatment group designated according to randomization by IVRS.
- Modified Intent-to-Treat (mITT) Population: it included all subjects who met eligibility criteria, experienced no protocol violations during the study, and received a minimum of 1 cycle of treatment. It was used for sensitivity analysis of primary and secondary efficacy endpoints, with treatment group designated according to randomization by IVRS.
- CR population: defined all patients whose first response after induction was CR. This is defined by FDA and not in the SAP.
- CRi population: defined as all patients whose first response after induction was CRi. This is defined by FDA and not in the SAP.
- Safety Population: it included all randomized subjects who received at least 1 dose of study treatment. Unless specified otherwise, it was used for drug exposure and safety analysis, with treatment group designated according to the actual treatment received.

Analysis Methods for Primary Endpoint OS

The primary analysis for OS is a stratified log-rank test performed on ITT population. The stratification variables are age at time of induction therapy, cytogenetic risk category at time of induction therapy, prior history of MDS and received consolidation therapy following induction therapy. The SAP pre-specified that if a stratum contained less than 16 subjects, then only three stratification variables that result in the largest minimum stratum size will be used for analysis purpose. The HR and its 95% confidence interval (CI) will be estimated using a stratified Cox proportional hazards model.

For subjects who survived at the end of follow-up period, or withdrew consent, or were lost to follow up, OS will be censored at the last known alive date or the consent withdrawal date.
The following sensitivity analysis will be conducted for OS:

- Primary analysis performed on mITT population;
- Censoring for the use of any subsequent therapy (including post-treatment transplant) for AML;
- 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;
- Not censoring for withdrawal of consent;
- Cox proportional hazard model with covariates adjustment will include, but not limited to, treatment, baseline characteristics (such as age, ECOG score, cytogenetic risk status, CR/CRi status at randomization, etc.), subsequent AML therapy as time-varying covariate and treatment-by-subsequent AML therapy interaction;
- Inverse probability of censoring weighted (IPCW) method.
- Regression based imputation analysis method that allows for inferences about the treatment effect in the presence of confounding due to additional therapy received subsequent to the study treatment.
- Restricted mean survival time (RMST);
- Piecewise Cox proportional hazard model with cutoff time points: 3, 6, and 12 months.

The following subgroup analysis will be conducted for OS:

- Age at induction therapy (< 65, ≥ 65, ≥ 75 years);
- Sex (male, female);
- Race (White, Asian, Black or Others);
- CR/CRi status at randomization (CR, CRi);
- CR/CRi status at first achieving response (CR, CRi);
- Consolidation therapy following induction (yes, no);
- Consolidation therapy following induction (1 or 2 cycles, 3 or 4 cycles);
- CR/CRi status at randomization and use of consolidation (CR with consolidation, CR without consolidation, CRi with consolidation, and CRi without consolidation);
- MRD status at randomization (positive, negative);
- CR/CRi status at randomization and MRD status at randomization (CR with MRD positive, CR with MRD negative, CRi with MRD positive, and CRi with MRD negative);
- Prior history of MDS or CMML (yes, no);
- Cytogenetic risk category at induction therapy (intermediate, poor);
- Geographic region (North America, Europe, Asia and Australia);
- ECOG performance status (0 or 1, 2 or 3);
- WHO AML classification (AML with myelodysplasia-related changes, AML with recurrent genetic abnormalities, AML not otherwise specified);
- Types of first line subsequent therapy (high intensity, low intensity chemotherapy, hypomethylating agent (HMA) monotherapy or other non-HMA subsequent therapy, Azacitidine monotherapy or other subsequent therapy (excluding decitabine monotherapy)).

Analysis Methods for Key Secondary Endpoint RFS

The analysis for RFS is the same as OS. To preserve the overall alpha level of 0.05, formal statistical inference for RFS would not be made if the null hypothesis of OS was not rejected.

For subjects who were still alive without documented relapse or were lost to follow-up or withdrew consent without documented relapse, RFS was to be censored at the last bone marrow assessment date. The details of primary censoring rules are outlined in Table 18.

Table 18. Primary Censoring Rules for RFS

Situation	Derivation Rules	Situation Outcome
Either documented relapse or death	Define event date is earliest of: • Date of documented relapse • Date of death Calculate interval between the event date and the previous bone marrow assessment date or the randomization date (if no postbaseline bone marrow assessment). Note: The cutoff of 200 day is selected based on the following protocol specified schedule procedure: the 28-day treatment cycle has +/- 3 days window; bone marrow is expected to be conducted every 3 cycles (with +/- 7 day window). Thus, 31*3+7=100 days is considered within the window for any two consecutive scheduled assessments.	If interval ≤ 200 days, then: • Event, if no subsequent therapy for AML or subsequent therapy for AML is on or after event date. • Censor, if subsequent therapy for AML is before event date. Censor date is last bone marrow assessment on or before start of subsequent therapy for AML, or randomization date if no post-baseline bone marrow assessment prior to start of subsequent therapy for AML. If interval > 200 days, then: • Censor: Censor date is last bone marrow assessment date, or randomization date if no post-baseline bone marrow assessment prior to start of subsequent therapy for AML.
No documented relapse and no death		Censor: Censor date is last bone marrow assessment date, or randomization date if no post-baseline bone marrow assessment prior to start of subsequent therapy for AML.

Source: Table 2 in the Applicant's Statistical Analysis Plan on Page 30.

Statistical Reviewer's comment: The FDA definition of RFS is "time from randomization to relapse or death in patients with CR". This definition does not censor for subsequent therapy as the Applicant's definition does.

The following sensitivity analysis will be conducted for OS:

- Primary analysis performed on mITT population;
- Replacing RFS definition with the documented relapse based on investigator assessed response;
- Censoring based on EMA guidance. EMA censoring rules are as follows:
    - For patients who experienced documented relapse or death, define outcome as event and event date as the earliest of documented relapse or death;
    - For patients without documented relapse or death, define outcome as censoring and event date as the date of last bone marrow assessment or date of randomization if no post-baseline bone marrow assessment.

Statistical Reviewer's comment: The EMA censoring rule was used for FDA analysis.

The subgroup analysis for RFS will be the same as OS.

Analysis Methods for Additional Secondary Efficacy Endpoints

- Time to relapse
    - It is defined as the time from randomization to documented relapse.
    - The planned analysis is a competing risk model with death as competing risk for relapse.
    - Similar censoring rules as in primary analysis of RFS will be applied.

- Time to discontinuation from treatment
    - It is defined as the interval from randomization to discontinuation from Investigational product.
    - The primary analysis is a competing risk model with the following competing events:
        - 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
    - Subjects who are ongoing in treatment at the time of study closure will be censored at the date of last visit.

Formal testing was to be stopped after testing RFS per the SAP. Consequently, the additional secondary efficacy endpoints are descriptive only.

Protocol Amendments

Significant protocol amendments are summarized in Table 19. The SAP was finalized on 25 July 2019 with no subsequent amendments.

Table 19. Significant Amendments to Study CC-486-AML-001 (QUAZAR)

Amendment	Significant changes
Protocol Amendment 1 (29 Dec 2015)	• Modification of Inclusion Criterion #2 to allow patients with AML secondary to chronic myelomonocytic leukemia into the study • Modification of Inclusion Criterion #4 to amend the amount of time required for subjects to be in CR or CRi from 3 months to 4 months (±7 days) • Reduction of the number of bone marrow collections and analyses for CR/CRi assessment • Reduction in the number of clinical visits in a cycle beginning with Cycle 25
Protocol Amendment 2 (08 Nov 2018)	• Adding an extension phase (EP) to o Allow all subjects who are on treatment with CC-486 and demonstrating clinical benefit to continue to do so in EP o Allow all subjects who were discontinued from the treatment phase (irrespective of randomization arm) and continuing in Follow-up Phase, will be followed for survival for at least another 12 months, until death, withdrawal of consent, study closure or lost to follow-up

Study Results

Compliance with Good Clinical Practices

All studies in the CC-486 clinical development program included in this submission were conducted in accordance with the principles of Good Clinical Practice and were closely monitored by Applicant personnel or a contract organization for compliance to all aspects of the protocols.

Financial Disclosure

Financial disclosures were submitted for 4 investigators who received between $10-50k per person from Celgene. The clinical sites to which the investigators belonged enrolled (b) (6) (b) (6) patients out of a total of 472 patients enrolled on CC-486-AML-001 making the contribution to the study population (b) (6)% at each site.

Data Quality and Integrity

The data quality is acceptable. In general, the reviewers were able to perform independent review and confirm the Applicant's analysis results using the submitted datasets.

FDA independently adjudicated each patient's baseline hematologic disease status at screening using the ADLB and ADMLL data files. FDA's final adjudications are included in Table 13. Disease Characteristics (ITT).

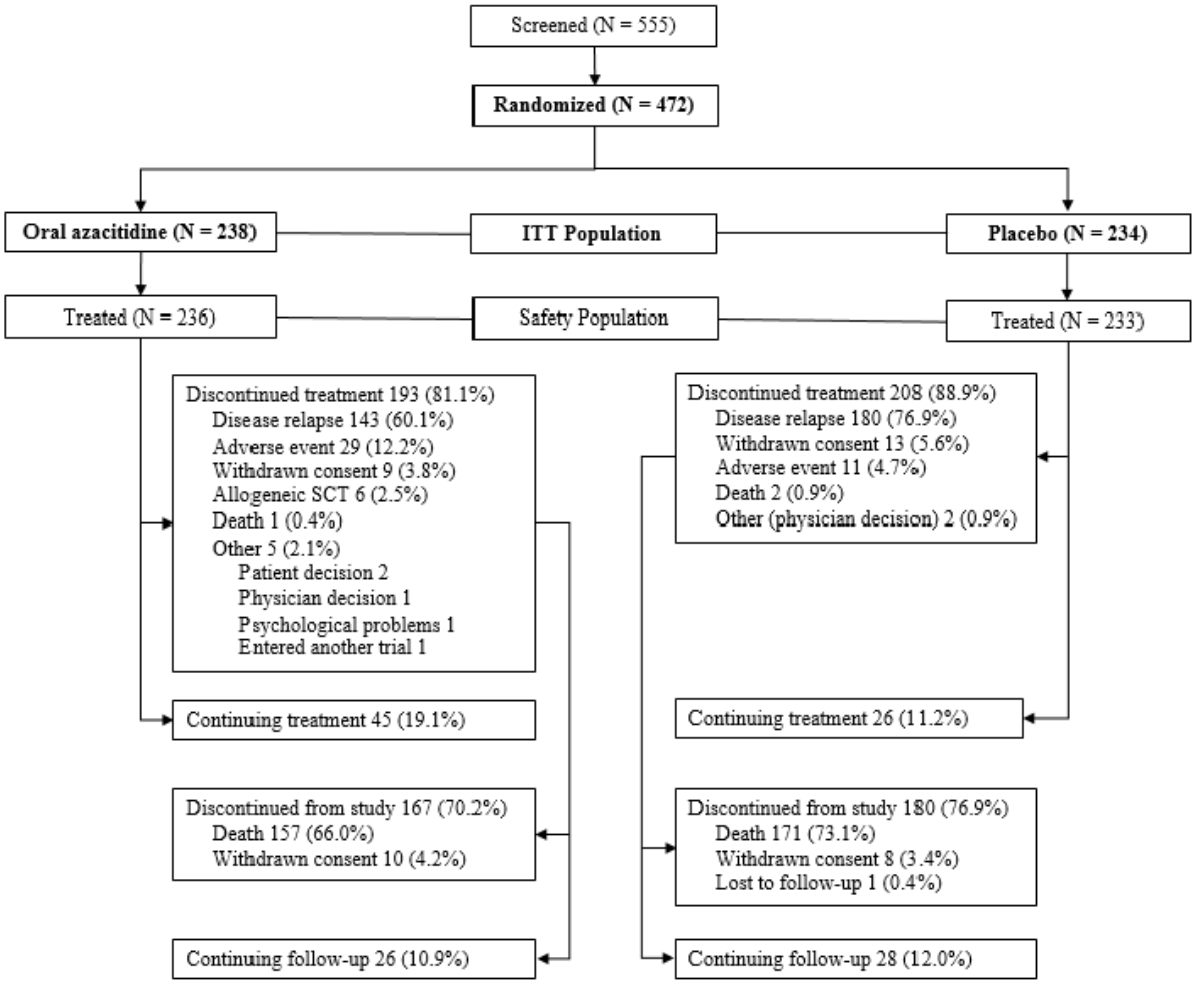
Due to the COVID pandemic, the on-site inspections of clinical sites 902 and 500 could not be performed (see Section 4.1). A post-hoc analysis of OS excluding the patients at these two sites was consistent with the findings for the overall trial (HR 0.69 in both cases).

Clinical TL Review Comment: Based on the analysis with clinical sites 902 and 500 excluded, the results from these two sites are unlikely to alter the final conclusions regarding the acceptability of the NDA submission.

Patient Disposition

A total of 555 patients were screened, of which 472 patients were randomized and included in the ITT population (234 subjects in placebo arm and 238 patients in Oral AZA arm). The patients disposition and discontinuation summary are shown in Figure 14. As of the 15 Jul 2019 data cut, 26 patients remained on placebo and 45 patients remained on Oral AZA treatment.

Figure 14. Study CC-486-AML-001: Patient Disposition



Source: Figure 2 in the Applicant's Clinical Study Report on Page 75.

Protocol Violations/Deviations

There were 53 (22 in Oral AZA arm and 31 in Placebo arm) patients with at least one protocol violation. The most frequently reported protocol violations were Investigator safety reporting (Oral AZA: 6%; Placebo: 9%), ICF process/timing issues (1% each group) and study procedures/assessments (Oral AZA: 1%; Placebo: 2%).

Statistical Reviewer's comment: The protocol deviations are largely administrative and therefore unlikely to have an appreciable effect on efficacy.

Patient Characteristics

Demographics

In the ITT population (N=472), the median age at induction was 68 years, 52% were male, and 88% were White, 84% were not Hispanic or Latino. Most subjects (67%) were from Europe, followed by North America (17%) and other regions (17%). Demographic characteristics were balanced between treatment arms (Table 20).

Table 20. CC-486-AML-001: Demographics (ITT)

Demographic Parameters	Category/Statistics	Placebo N=234	Oral AZA N=238	Total N=472
Age at ICF (years)	n	234	238	472
	Mean (SD)	68 (5.6)	67.9 (5.7)	67.9 (5.7)
	Median (Min, Max)	68 (55, 82)	68 (55, 86)	68 (55, 86)
Age Category at ICF, n (%)	>=55 to <65 years	68 (29%)	66 (28%)	134 (28%)
	>=65 to <75 years	142 (61%)	144 (61%)	286 (61%)
	>=75 to <85 years	24 (10%)	27 (11%)	51 (11%)
	>=85 years	0	1 (0%)	1 (0%)
Age Category at Induction, n (%)	55-64 years	70 (30%)	70 (29%)	140 (30%)
	>=65 years	164 (70%)	168 (71%)	332 (70%)
Sex, n (%)	Male	127 (54%)	118 (50%)	245 (52%)
	Female	107 (46%)	120 (50%)	227 (48%)
Race, n (%)	White	197 (84%)	216 (91%)	413 (88%)
	Asian	20 (9%)	6 (3%)	26 (6%)
	Black or African American	6 (3%)	2 (1%)	8 (2%)
	Other	11 (5%)	12 (5%)	23 (5%)
	Not reported	0	2 (1%)	2 (0%)
Ethnicity, n (%)	Not Hispanic or Latino	202 (86%)	196 (82%)	398 (84%)
	Hispanic or Latino	14 (6%)	20 (8%)	34 (7%)
	Unknown	18 (8%)	22 (9%)	40 (8%)
Geographic Region, n (%)	Europe	147 (63%)	167 (70%)	314 (67%)
	North America	42 (18%)	37 (16%)	79 (17%)
	Australia	23 (10%)	26 (11%)	49 (10%)
	Asia	17 (7%)	6 (3%)	23 (5%)
	South America	5 (2%)	2 (1%)	7 (1%)

Source: Reviewer's analysis.

Other Baseline Characteristics

Table 21 and Table 22 summarize disease characteristics and baseline laboratory test results in the ITT population. Most had de novo AML (91%), had AML not otherwise specified (62%), had no prior history of MDS/CMML (92%), had intermediate cytogenetic risk at diagnosis (86%), had an ECOG score of 0 or 1 (92%), were ineligible for transplant due to age (65%) and received consolidation therapy (80%). About half (52%) of subjects were MRD negative at randomization. The median time since original AML diagnosis to randomization was 4.2 months (range: 1.4 to 10.9).

All subjects in the ITT population achieved CR (81%) or CRi (19%) after induction therapy. The median time since induction to randomization was 4 months (range: 1.3 to 15.1). The median time from induction to CR/CRi and from CR/CRi to randomization were 35 days (range: 13, 455) and 85 days (range: 7, 263) respectively. 76% remained at CR status at baseline and 20% at CRi. Disease characteristics and baseline laboratory test results for the ITT population were generally similar between treatment groups.

Table 21. CC-486-AML-001: Disease Characteristics (ITT)

Disease Characteristics	**Category/Statistics**		**Placebo N=234**	**Oral AZA N=238**	**Total N=472**
Initial AML Classification, n (%)	AML with recurrent genetic abnormalities		46 (20%)	39 (16%)	85 (18%)
	AML with myelodysplasia-related changes		42 (18%)	49 (21%)	91 (19%)
	Therapy related myeloid neoplasms		0	2 (1%)	2 (0%)
	AML not otherwise specified		145 (62%)	148 (62%)	293 (62%)
	Not reported		1 (0%)	0	1 (0%)
Type of AML, n (%)	Primary		216 (92%)	213 (89%)	429 (91%)
	Secondary		18 (8%)	25 (11%)	43 (9%)
MDS/CMML History, n (%)	Yes	Primary	17 (7%)	20 (8%)	37 (8%)
		Not reported	0	2 (1%)	2 (0%)
		Secondary	0	0	0
	No		217 (93%)	216 (91%)	433 (92%)
ECOG Performance Status, n (%)	Grade 0		111 (47%)	116 (49%)	227 (48%)
	Grade 1		106 (45%)	101 (42%)	207 (44%)
	Grade 2		15 (6%)	21 (9%)	36 (8%)
	Grade 3		2 (1%)	0	2 (0%)
Cytogenetic Risk Assessment, n (%)	Intermediate risk		203 (87%)	203 (85%)	406 (86%)
	Poor risk		31 (13%)	35 (15%)	66 (14%)
MRD Status[1] at Rand., n (%)	Negative		111 (47%)	133 (56%)	244 (52%)
	Positive		116 (50%)	103 (43%)	219 (46%)
	Not reported		7 (3%)	2 (1%)	9 (2%)

Disease Characteristics	Category/Statistics		Placebo N=234	Oral AZA N=238	Total N=472
Reason Ineligible for Transplant[2], n (%)	Age		152 (65%)	154 (65%)	306 (65%)
	Comorbidities		50 (21%)	52 (22%)	102 (22%)
	Performance status		9 (4%)	14 (6%)	23 (5%)
	Unavailable donor		35 (15%)	37 (16%)	72 (15%)
	Subject decision		32 (14%)	19 (8%)	51 (11%)
	Unfavorable cytogenetics		10 (4%)	6 (3%)	16 (3%)
	Others		21 (9%)	28 (12%)	49 (10%)
Prior Consolidation Therapy, n (%)	Yes	1 cycle	102 (44%)	110 (46%)	212 (45%)
		2 cycles	77 (33%)	70 (29%)	147 (31%)
		3 cycles	13 (6%)	6 (3%)	19 (4%)
	No		42 (18%)	52 (22%)	94 (20%)
First Response Type, n (%)	CR		197 (84%)	187 (79%)	384 (81%)
	CRi		37 (16%)	51 (21%)	88 (19%)
Response Status at Baseline Provided by Applicant, n (%)	CR		177 (76%)	183 (77%)	360 (76%)
	CRi		44 (19%)	50 (21%)	94 (20%)
	Not CR/CRi		11 (5%)	5 (2%)	16 (3%)
	Not Reported		2 (1%)	0	2 (0%)
Response Status at Baseline per FDA Adjudication, n (%)	CR		181 (77%)	185 (78%)	366 (78%)
	CRi		38 (16%)	44 (18%)	82 (17%)
	Not CR/CRi		13 (6%)	9 (4%)	24 (5%)
	Not Reported		2 (1%)	0	2 (0%)
Baseline Bone Marrow % of Blasts	n		232	238	470
	Mean (SD)		2.2 (1.5)	2.1 (1.5)	2.2 (1.5)
	Median (Min, Max)		2 (0, 6.5)	2 (0, 5)	2 (0, 6.5)
Baseline Peripheral Blood % of Blasts	n		222	230	452
	Mean (SD)		0 (0.3)	0.1 (0.3)	0.1 (0.3)
	Median (Min, Max)		0 (0, 2)	0 (0, 2)	0 (0, 2)
Time from AML Diagnosis to Rand., months	n		234	237	471
	Mean (SD)		4.3 (1.2)	4.4 (1.3)	4.3 (1.3)
	Median (Min, Max)		4.2 (1.4, 10.9)	4.2 (1.5, 9.2)	4.2 (1.4, 10.9)
Time from Induction to Rand., months	n		232	237	469
	Mean (SD)		4.1 (1.4)	4 (1.2)	4.1 (1.3)
	Median (Min, Max)		4 (1.3, 15.1)	4 (1.4, 8.8)	4 (1.3, 15.1)
Time from Induction to First Achieving CR/CRi, days	n		232	237	469
	Mean (SD)		45 (36.5)	46.2 (28.5)	45.6 (32.7)
	Median (Min, Max)		35 (14, 455)	36 (13, 242)	35 (13, 455)
Time from First Achieving CR/CRi to Rand., days	n		234	238	472
	Mean (SD)		81 (32.2)	78.1 (30.1)	79.5 (31.2)
	Median (Min, Max)		86 (7, 263)	84.5 (7, 154)	85 (7, 263)

[1] MRD at screening was provided as a Research Use Only assay developed by (b) (4)
An analytical MRD method summary report was provided in Module 5.3.1.4.
[2] A subject may have multiple reasons ineligible for transplant.

Source: Reviewer's analysis

Table 22. CC-486-AML-001: Baseline Laboratory Test Results (ITT)

Variable	Category/Statistics	Placebo N=234	Oral AZA N=238	Total N=472
Hemoglobin, g/dL	n	234	238	472
	Mean (SD)	109.3 (14.5)	113.2 (15.6)	111.3 (15.2)
	Median (Min, Max)	108 (77, 149)	113 (75, 159)	111 (75, 159)
Platelet, 10^9/L	n	234	238	472
	Mean (SD)	184.5 (104.5)	180 (115.3)	182.2 (110)
	Median (Min, Max)	178.5 (16, 636)	154 (22, 801)	165 (16, 801)
Platelet x 10^9/L, n (%)	< 20	1 (0%)	0	1 (0%)
	>= 20 to < 50	16 (7%)	12 (5%)	28 (6%)
	>= 50 to < 100	27 (12%)	36 (15%)	63 (13%)
	>= 100	190 (81%)	190 (80%)	380 (81%)
ANC, 10^9/L	n	233	237	470
	Mean (SD)	3.1 (1.8)	3.3 (2.1)	3.2 (1.9)
	Median (Min, Max)	2.8 (0.5, 9.6)	3 (0.3, 15.9)	2.9 (0.3, 15.9)
ANC x 10^9/L, n (%)	< 0.5	1 (0%)	1 (0%)	2 (0%)
	>= 0.5 to < 1.0	17 (7%)	7 (3%)	24 (5%)
	>= 1.0	215 (92%)	229 (96%)	444 (94%)
	Not reported	1 (0%)	1 (0%)	2 (0%)
WBC, 10^9/L	n	234	238	472
	Mean (SD)	4.9 (2.2)	5.2 (2.5)	5.1 (2.3)
	Median (Min, Max)	4.5 (1.3, 12.6)	4.9 (0.8, 18.7)	4.7 (0.8, 18.7)
WBC x 10^9/L, n (%)	< 5	139 (59%)	126 (53%)	265 (56%)
	>= 5	95 (41%)	112 (47%)	207 (44%)

Source: Reviewer's analysis.

Table 23. CC-486-AML-001: Prior Induction (ITT)

ATC Dictionary Level Preferred Name	Placebo N=234	Oral AZA N=238	Total N=472
Antineoplastic and immunomodulating agents			
Cytarabine	232 (99%)	237 (100%)	469 (99%)
Idarubicin	130 (56%)	129 (54%)	259 (55%)
Daunorubicin	77 (33%)	79 (33%)	156 (33%)
Mitoxantrone	18 (8%)	27 (11%)	45 (10%)
Fludarabine	24 (10%)	25 (11%)	49 (10%)
Etoposide	20 (9%)	21 (9%)	41 (9%)
Hydroxycarbamide	12 (5%)	11 (5%)	23 (5%)
Daunorubicin hydrochloride	7 (3%)	5 (2%)	12 (3%)
Idarubicin hydrochloride	5 (2%)	6 (3%)	11 (2%)
Mitoxantrone hydrochloride	2 (1%)	3 (1%)	5 (1%)
Various			
Investigational drug	0	5 (2%)	5 (1%)

Source: Reviewer's analysis.

Table 24. CC-486-AML-001: Prior Consolidation (ITT)

ATC Dictionary Level Preferred Name	Placebo N=234	Oral AZA N=238	Total N=472
Antineoplastic and immunomodulating agents			
Cytarabine	191 (82%)	186 (78%)	377 (80%)
Idarubicin	44 (19%)	51 (21%)	95 (20%)
Daunorubicin	15 (6%)	22 (9%)	37 (8%)
Mitoxantrone	15 (6%)	11 (5%)	26 (6%)
Fludarabine	13 (6%)	10 (4%)	23 (5%)
Etoposide	7 (3%)	7 (3%)	14 (3%)
Filgrastim	2 (1%)	0	2 (0%)
Gemtuzumab ozogamicin	2 (1%)	1 (0%)	3 (1%)
Cladribine	1 (0%)	0	1 (0%)
Clofarabine	1 (0%)	0	1 (0%)
Granulocyte colony stimulating factor	1 (0%)	1 (0%)	2 (0%)
Methotrexate	1 (0%)	0	1 (0%)
Tioguanine	1 (0%)	1 (0%)	2 (0%)
Tretinoin	1 (0%)	0	1 (0%)
Daunorubicin hydrochloride	0	1 (0%)	1 (0%)
Mitoxantrone hydrochloride	0	1 (0%)	1 (0%)
Missing	0	1 (0%)	1 (0%)
Systemic hormonal preparations, excluding sex hormones and insulins			
Dexamethasone	2 (1%)		2 (0%)

Source: Reviewer's analysis.

Concomitant Medications and Treatment Compliance

Table 25 summarizes study drug treatment compliance. Mean compliance rates were 95% and median 100% in both arms.

Table 25. CC-486-AML-001: Study Drug Treatment Compliance (ITT)

Parameter	Category/Statistics	Placebo N=234	Oral AZA N=238	Total N=472
Overall Compliance, %	n	233	236	469
	Mean (SD)	95.4 (9.2)	94.7 (14.6)	95.1 (12.2)
	Median (Min, Max)	100 (42.9, 117.9)	100 (7.1, 101.1)	100 (7.1, 117.9)
Compliance Category, n (%)	< 75%	10 (4%)	14 (6%)	24 (5%)
	75%-120%	223 (96%)	222 (94%)	445 (95%)
	> 120%	0	0	0

Source: Reviewer's analysis.

Treatment compliance is shown by cycle number and dose intensity (% of full planned dose for the cycle) in Table 19.

Table 26. CC-486-AML-001: Summary of Dose Intensity by Cycle (Cycles 1-12)

	CC-486				Placebo			
		Dose Intensity Category				Dose Intensity Category		
Cycle	N*	<80%	80-100%	>100%	N*	<80%	80-100%	>100%
1	236	16 (6.8)	220 (93.2)	0	233	7 (3.0)	223 (95.7)	3 (1.3)
2	222	26 (11.7)	195 (87.8)	1 (0.5)	217	12 (5.5)	204 (94.0)	1 (0.5)
3	204	26 (12.7)	172 (84.3)	6 (2.9)	195	15 (7.7)	173 (88.7)	7 (3.6)
4	196	27 (13.8)	159 (81.1)	10 (5.1)	169	9 (5.3)	153 (90.5)	7 (4.1)
5	186	31 (16.7)	148 (79.6)	7 (3.8)	154	14 (9.1)	136 (88.3)	4 (2.6)
6	174	33 (19.0)	134 (77.0)	7 (4.0)	135	15 (11.1)	116 (85.9)	4 (3.0)
7	162	28 (17.3)	125 (77.2)	9 (5.6)	113	3 (2.7)	104 (92.0)	6 (5.3)
8	156	28 (17.9)	120 (76.9)	8 (5.1)	107	4 (3.7)	96 (89.7)	7 (6.5)
9	148	30 (20.3)	108 (73.0)	10 (6.8)	93	6 (6.5)	79 (84.9)	8 (8.6)
10	135	29 (21.5)	98 (72.6)	8 (5.9)	84	3 (3.6)	73 (86.9)	8 (9.5)
11	131	31 (23.7)	92 (70.2)	8 (6.1)	81	2 (2.5)	73 (90.1)	6 (7.4)
12	125	36 (28.8)	78 (62.4)	11 (8.8)	74	5 (6.8)	64 (86.5)	5 (6.8)

* N is number of patients starting the cycle

Source: Applicant Response to IR dated 09 June 2020 (SDN 0018)

Concomitant medications were assessed as recorded in the ADCM data file. Of concomitant medications taken by 99.6% of patients, the use of concomitant medications received were comparable between treatments. The concomitant medications used most commonly (≥ 25%) while on-treatment were antiemetics, antibiotics, drugs for acid-related disorders, analgesics, drugs for functional gastrointestinal disorders, antidiarrheal agents, diuretics, and mineral supplements.

Per protocol, antiemetic medication was to be administered 30 minutes prior to each inpatient dose. If there had been no nausea/vomiting, the Investigator could choose to omit antiemetic as required, provided this was documented in the CRF. In patients not having problems during the first two cycles, the treating physician could discontinue use of antiemetic medications. Actual use of prophylactic antiemetics is shown below.

Table 27. CC-486-AML-001: Prophylactic[a] Antiemetic Use by Cycle (Cycles 1-5)

Cycle	Oral Azacitidine		Placebo	
• Cycle 1	161/236	68%	118/233	51%
• Cycle 2	90/222	41%	36/217	17%
• Cycle 3	81/204	40%	22/195	11%
• Cycle 4	72/196	63%	22/169	13%
• Cycle 5	68/186	37%	14/154	9%

Source: FDA Analysis

[a] Prophylaxis inferred if CMINDC ≈ prophylaxis, pre-treatment, prevention, treatment and prophylaxis

Subsequent AML therapies

Table 28 and Table 29 summarize subsequent therapy and first subsequent regimen respectively. 58% subjects in Oral AZA arm and 73% in Placebo arm received at least one subsequent AML therapy. The most frequently reported subsequent AML therapies were in the ATC classes of antineoplastic and immune modulating agents (Oral AZA: 56%; Placebo: 72%).

54% subjects in Oral AZA arm and 68% in Placebo arm received at least one first subsequent AML therapy. 18% subjects received hypomethylating agent (Oral AZA: 13%; Placebo: 23%).

Table 28. CC-486-AML-001: Subsequent AML Therapies (ITT)

Treatment	Placebo N=234	Oral AZA N=238	Total N=472
Stem Cell Transplantation	15 (6%)	32 (14%)	47 (10%)
Other type of AML therapy			
Intensive chemotherapy	88 (38%)	69 (29%)	157 (33%)
Low-intensity therapy	110 (47%)	94 (39%)	204 (43%)
Other	19 (8%)	15 (6%)	34 (7%)
Not reported	1 (0%)	0	1 (0%)
Subsequent AML therapies reported for ≥ 10% of subjects in either treatment group[1]			
Antineoplastic and immunomodulating agents			
Cytarabine	92 (39%)	83 (35%)	175 (37%)
Fludarabine	48 (21%)	32 (13%)	80 (17%)
Azacitidine	47 (20%)	31 (13%)	78 (17%)
Hydroxycarbamide	34 (15%)	28 (12%)	62 (13%)
Idarubicin	33 (14%)	20 (8%)	53 (11%)

Source: Reviewer's analysis.
[1] ATC Dictionary Level and Preferred Name

Table 29. CC-486-AML-001: First Subsequent Regimens for AML (ITT)

	Placebo N=234	Oral AZA N=238	Total N=472
Type of therapy			
Intensive chemotherapy	79 (34%)	62 (26%)	141 (30%)
Low-intensity therapy	77 (33%)	65 (27%)	142 (30%)
Other	3 (1%)	2 (1%)	5 (1%)
Not reported	1 (0%)	0	1 (0%)
Hypomethylating Agent	54 (23%)	32 (13%)	86 (18%)
Azacitidine	37 (16%)	21 (9%)	58 (12%)
Decitabine	16 (7%)	11 (5%)	27 (6%)
Guadecitabine	1 (0%)	0	1 (0%)

Source: Reviewer's analysis.

Efficacy Results

Efficacy Results – Primary Endpoint OS

According to the analysis plan prespecified in the SAP, the stratification factor prior history of MDS was dropped in the primary analysis and three stratification variables (age, cytogenetic risk category, and consolidation therapy) were used in stratified analysis, because some strata would have < 16 subjects when four stratification factors were used.

As of the 15 Jul 2019 data cut, 158 (66%) subjects in Oral AZA arm and 171 (73%) in Placebo arm experienced the event of death. Oral AZA demonstrated an OS advantage with a hazard ratio (HR) of 0.69 (95% CI: 0.55, 0.86) and p-value of 0.0009. The median OS was 24.7 months for Oral AZA arm and 14.8 months for Placebo arm. There were 80 (34%) subjects in Oral AZA arm and 63 (27%) in Placebo arm who were censored, and reasons for censoring were similar between treatment arms.

Table 30 and Figure 15 provide a summary of OS for the ITT population.

The median follow-up was 11.9 months (range: 0.5, 63.2), 14.5 months (range: 0.5, 63.2) and 10.4 months (range: 1.1, 62.5) in Oral AZA and Placebo arm respectively.

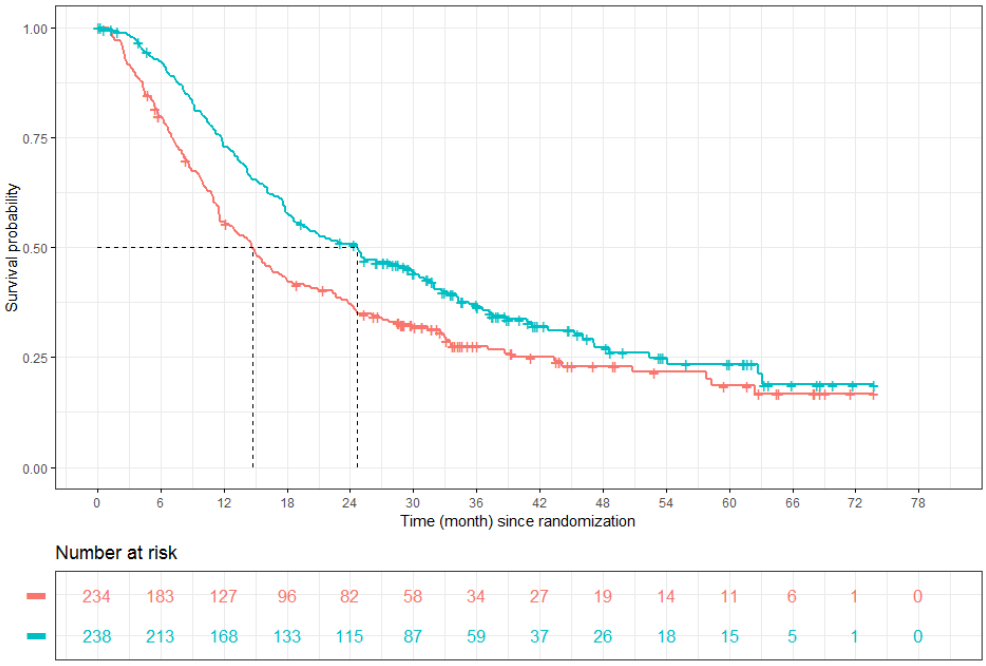
Table 30. CC-486-AML-001: Summary of OS (ITT)

Parameter	**Placebo N=234**	**Oral AZA N=238**
Subjects with event (death), n (%)	171 (73)	158 (66)
Subjects censored, n (%)	63 (27)	80 (34)
Median (95% CI)[1]	14.8 (11.7, 17.6)	24.7 (18.7, 30.5)
Hazard Ratio (95% CI)[2]	0.69 (0.55, 0.86)	
p value[2]	0.0009	

[1] Confidence intervals (CI) were calculated via the survival function itself without any logarithm transformation.
[2] Estimated with Cox proportional hazard model and log-rank test stratified by age at time of induction therapy (55 to 64 vs. ≥65 years), cytogenetic risk category at time of induction therapy (intermediate risk vs. poor risk) and received consolidation therapy following induction therapy (yes vs. no).

Source: Reviewer's analysis.

Figure 15. CC-486-AML-001: Kaplan-Meier Plot of OS for CC-486 versus Placebo (ITT)



Source: Reviewer's analysis.

Statistical Reviewer's comment: The Applicant presented landmark analyses reporting 0.5, 1, 2-year OS by treatment arm. Landmark analyses may not be appropriate summary measures, because the choice of such landmark times is arbitrary. In addition, these times are specific to the population enrolled in Study CC-486-AML-001 and not likely to meaningfully estimate such quantities in the broader AML population.

Efficacy Results – Key Secondary Endpoint RFS

While the Applicant defines RFS as "time from randomization relapse or death", FDA defines RFS as "time from CR to relapse or death" for patients who achieved CR after induction, i.e., RFS is measurable only in the CR population. Table 31 and Figure 16 present the summary of RFS per Applicant vs FDA definition for the ITT population and CR population respectively.

As a subset of ITT population, the CR population consists of 366 (78%) subjects who achieved CR after induction, 185 (78%) and 181 (77%) in Oral AZA and Placebo arm respectively. 145 (78%) and 156 (86%) subjects experienced the event of relapse or death in Oral AZA and Placebo arm respectively.

The results from Cox proportional hazards model and log-rank test were similar between RFS per Applicant definition and RFS per FDA definition: HR = 0.64 (95% CI: 0.52, 0.79) and p-value of < 0.0001, and HR = 0.66 (95% CI: 0.53, 0.84) and p-value of 0.0005, respectively. The median was 10.2 and 4.8 months for Oral AZA and Placebo arm respectively per Applicant definition, and 12.8 and 7.8 months for Oral AZA and Placebo arm respectively per FDA definition. Among the CR

population, there were 40 (22%) subjects in Oral AZA arm and 25 (14%) in Placebo arm who were censored, and reasons for censoring were similar between treatment arms.

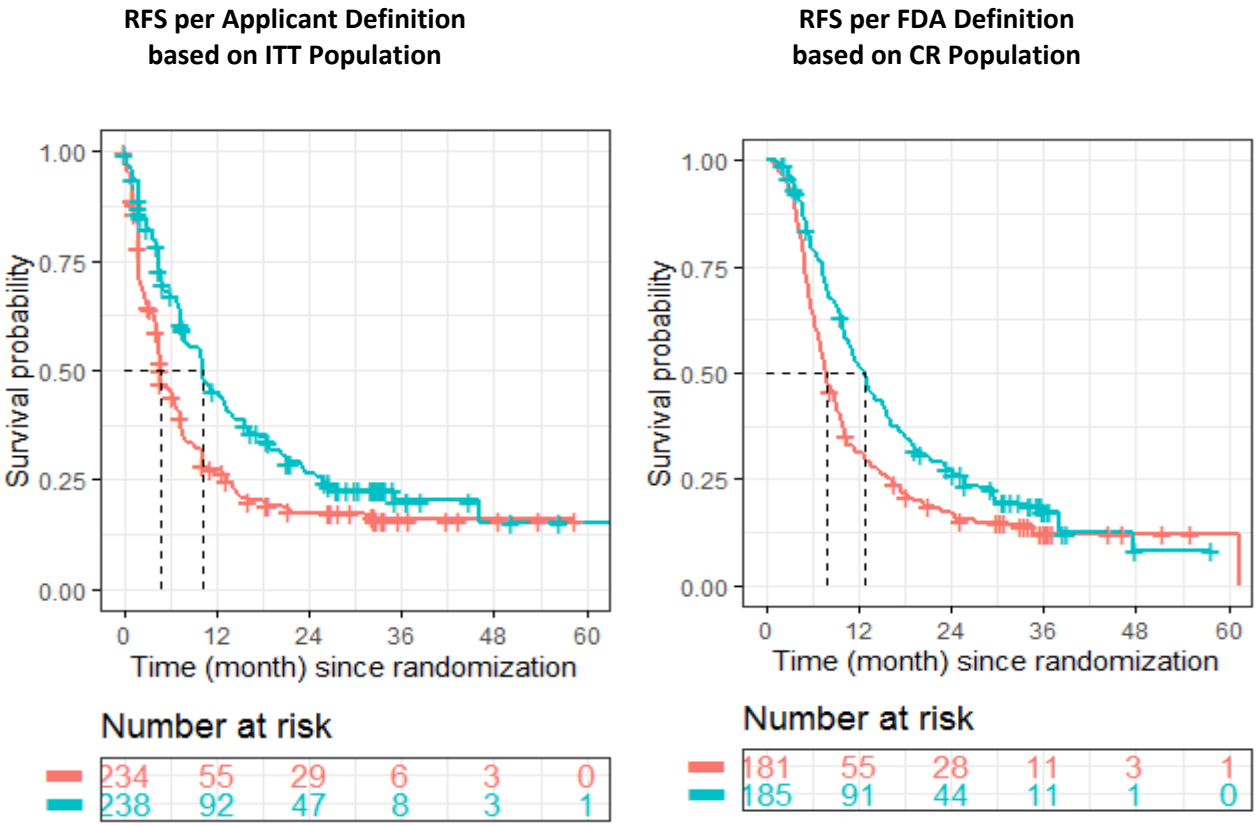
Table 31. CC-486-AML-001: Summary of RFS by Applicant and FDA Definitions

	RFS per Applicant Definition based on ITT Population		RFS per FDA Definition based on CR Population	
Parameter	Placebo N=234	Oral AZA N=238	Placebo N=181	Oral AZA N=185
Subjects with events, n (%)	181 (77)	164 (69)	156 (86%)	145 (78%)
Subjects censored, n (%)	53 (23)	74 (31)	25 (14%)	40 (22%)
Median (95% CI)[1]	4.8 (4.6, 6.4)	10.2 (7.9, 12.9)	7.8 (7.1, 9.2)	12.8 (10.6, 15.2)
Hazard Ratio (95% CI)[2]	0.64 (0.52, 0.79)		0.66 (0.53, 0.84)	
p-value[2]	<0.0001		0.0005	

[1] Confidence intervals (CI) were calculated via the survival function itself without any logarithm transformation.
[2] Estimated with Cox proportional hazard model and log-rank test stratified by age at time of induction therapy (55 to 64 vs. ≥65 years), cytogenetic risk category at time of induction therapy (intermediate risk vs. poor risk) and received consolidation therapy following induction therapy (yes vs. no).

Source: Reviewer's analysis.

Figure 16. CC-486-AML-001: Kaplan-Meier Plot of RFS for CC-486 versus Placebo



Source: Reviewer's analysis.

Analysis Methods for Additional Secondary Efficacy Endpoints

Time to Relapse

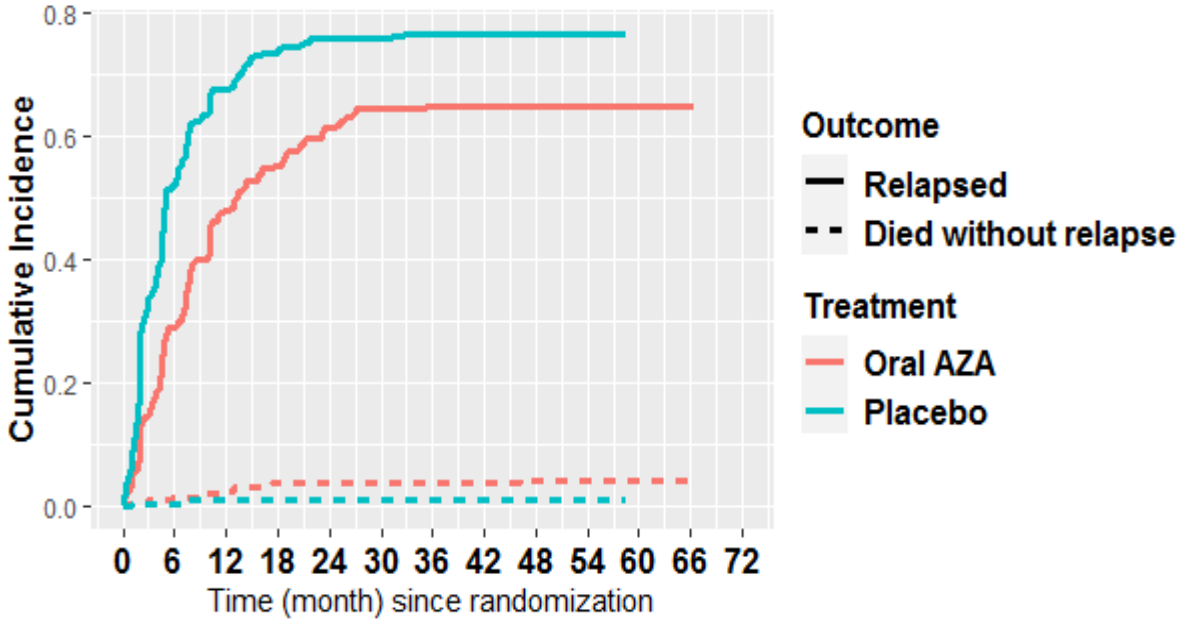
There were 154 (65%) subjects in Oral AZA arm and 179 (77%) in Placebo arm who had a programmatically-derived documented relapse; 10 (4.2%) in Oral AZA arm and 2 (0.9%) in Placebo arm subjects died without documented relapse. A summary of time to relapse and the cumulative incidence distribution is presented in Table 32 and Figure 17.

Table 32. CC-486-AML-001: Summary of Time to Relapse (ITT)

Parameter	Placebo N=234	Oral AZA N=238
Subjects relapsed, n (%)	179 (77)	154 (65)
Subjects died without relapse, n (%)	2 (1)	10 (4)
Subjects censored, n (%)	53 (23)	74 (31)
[1] Estimated based on the cumulative incidence function from a competing risk analysis with death as a competing risk for relapse.		

Source: Reviewer's analysis.

Figure 17. CC-486-AML-001: Cumulative Incidence Distribution of Time to Relapse (ITT)



Source: Reviewer's analysis.

Time to Treatment Discontinuation

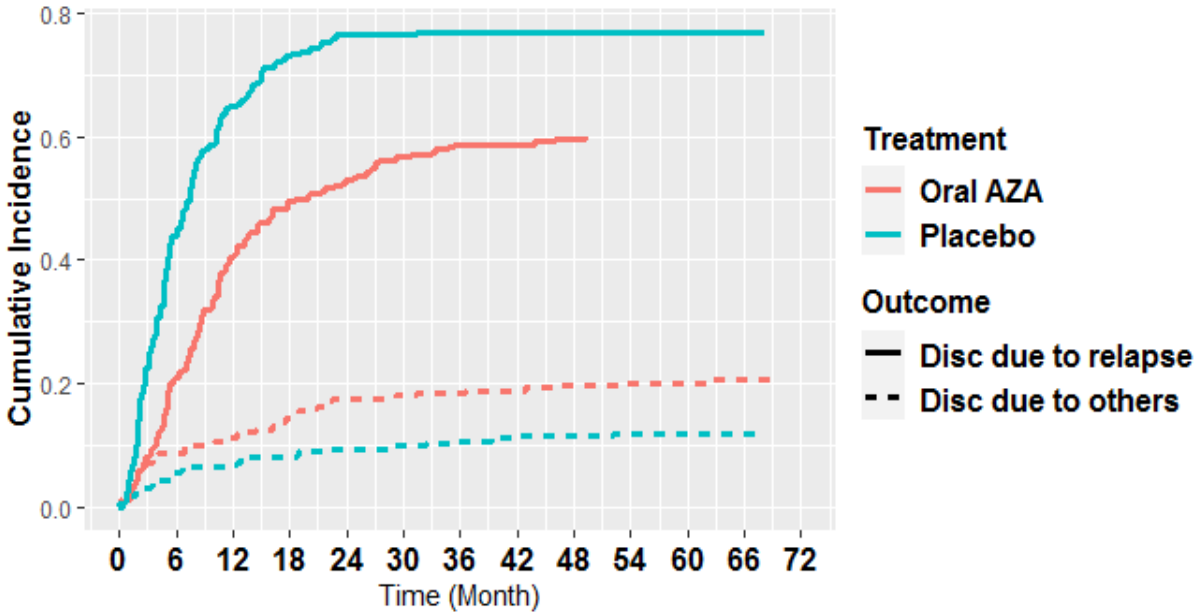
193 (81%) subjects in Oral AZA arm and 208 (89%) in Placebo arm had discontinued study treatment. Among them, 143 (60%) and 180 (77%) subjects discontinued treatment due to disease relapse in Oral AZA and Placebo arm respectively. It appears that Oral AZA arm remained on treatment for a longer period of time than Placebo arm. Summary of Time to treatment discontinuation and the cumulative incidence distribution is presented in Table 33 and Figure 18.

Table 33. CC-486-AML-001: Summary of Time to Treatment Discontinuation Due to Disease Relapse (ITT)

Parameter	Placebo N=234	Oral AZA N=238
Subjects with treatment discontinuation, n (%)	208 (89)	193 (81)
Due to disease relapse	180 (77)	143 (60)
Due to adverse event	11 (5)	29 (12)
Due to eligibility for bone marrow or stem cell transplant	0	6 (3)
Due to death	2 (1)	1 (0)
Due to other	15 (6)	14 (6)
Subjects censored, n (%)	26 (11)	45 (19)
[1] Estimated based on the cumulative incidence function from a competing risk analysis with treatment discontinuation due to other reasons as competing risk.		

Source: Reviewer's analysis.

Figure 18. CC-486-AML-001: Time to Treatment Discontinuation Due to Disease Relapse (ITT)



Source: Reviewer's analysis.

Statistical Reviewer's comment: These analyses for "Time to Relapse" and "Time to Treatment Discontinuation" are descriptive only. Note that these models require strong

assumptions, namely that the risks are independent. In general, such an assumption is not likely to hold.

Subpopulations

The Applicant conducted subgroup analysis by demographics and disease-related characteristics (Figure 28, Figure 29, Figure 30 and Figure 31 in Appendix 15). Additional sensitivity analyses were conducted by the FDA reviewer as following:

- Subgroup analysis of OS by response status achieved after induction (CR, CRi). Results are presented in Table 34.
- Subgroup analysis of OS by FDA-adjudicated response status at baseline (CR, CRi). Results are presented in Table 35.
- Subgroup analysis by region (Europe, North America, Other). Results are presented in Table 37 for OS and Table 66 in Appendix 15 for RFS per Applicant definition.
- Subgroup analysis of OS by number of prior consolidation cycles (0, 1, 2, 3 cycles).
- Results are presented in Table x for OS and Table 67 in Appendix 15 for RFS per Applicant definition.

Table 34. CC-486-AML-001: Subgroup Analysis of OS by Response Status per Applicant Definition Achieved after Induction

	CR after Induction		CRi after Induction	
Parameter	**Placebo N=197**	**Oral AZA N=187**	**Placebo N=37**	**Oral AZA N=51**
Subjects with event (death), n (%)	142 (72%)	120 (64%)	29 (78%)	38 (75%)
Subjects censored, n (%)	55 (28%)	67 (36%)	8 (22%)	13 (25%)
Hazard Ratio (95% CI) [1]	0.71 (0.55, 0.9)		0.74 (0.45, 1.2)	
[1] Estimated with unstratified Cox proportional hazard model.				

Source: Reviewer's analysis.

Table 35. CC-486-AML-001: Subgroup Analysis OS by FDA-Adjudicated Response Status at Study Baseline

	CR at Baseline		CRi at Baseline	
Parameter	**Placebo N=181**	**Oral AZA N=185**	**Placebo N=38**	**Oral AZA N=44**
Subjects with event (death), n (%)	135 (75%)	124 (67%)	24 (63%)	29 (66%)
Subjects censored, n (%)	46 (25%)	61 (33%)	14 (37%)	15 (34%)
Hazard Ratio (95% CI) [1]	0.72 (0.56, 0.92)		0.87 (0.51, 1.5)	
[1] Estimated with unstratified Cox proportional hazard model.				

Source: Reviewer's analysis.

Table 36. CC-486-AML-001: Subgroup Analysis of OS by Number of Consolidation Cycles

	No Consolidation		1 Cycle of Consolidation		2 Cycles of Consolidation		3 Cycles of Consolidation	
Parameter	Placebo N=42	Oral AZA N=52	Placebo N=102	Oral AZA N=110	Placebo N=77	Oral AZA N=70	Placebo N=13	Oral AZA N=6
Subjects with event, n (%)	33 (79%)	36 (69%)	80 (78%)	79 (72%)	52 (68%)	39 (56%)	6 (46%)	4 (67%)
Subjects censored, n (%)	9 (21%)	16 (31%)	22 (22%)	31 (28%)	25 (32%)	31 (44%)	7 (54%)	2 (33%)
Hazard Ratio (95% CI) [1]	0.54 (0.33, 0.87)		0.73 (0.53, 1)		0.68 (0.44, 1.04)		0.99 (0.23, 4.25)	
Hazard Ratio (95% CI) [2]	0.55 (0.34, 0.89)		0.75 (0.55, 1.02)		0.69 (0.45, 1.04)		1.37 (0.37, 5.02)	

[1] Estimated with Cox proportional hazard model and log-rank test stratified by age at time of induction therapy (55 to 64 vs. ≥65 years), cytogenetic risk category at time of induction therapy (intermediate risk vs. poor risk) and received consolidation therapy following induction therapy (yes vs. no).
[2] Estimated with unstratified Cox proportional hazard model and log-rank test.

Source: Reviewer's analysis.

Table 37. CC-486-AML-001: Subgroup Analysis of OS by Geographic Region

	Europe		North America		Other	
Parameter	**Placebo N=147**	**Oral AZA N=167**	**Placebo N=42**	**Oral AZA N=37**	**Placebo N=45**	**Oral AZA N=34**
Subjects with event, n (%)	114 (78%)	111 (66%)	30 (71%)	29 (78%)	27 (60%)	18 (53%)
Subjects censored, n (%)	33 (22%)	56 (34%)	12 (29%)	8 (22%)	18 (40%)	16 (47%)
Hazard Ratio (95% CI) [1]	0.53 (0.41, 0.70)		1.18 (0.67, 2.09)		0.82 (0.43, 1.56)	
Hazard Ratio (95% CI) [2]	0.6 (0.46, 0.77)		1.09 (0.65, 1.82)		0.9 (0.5, 1.64)	

[1] Estimated with Cox proportional hazard model and log-rank test stratified by age at time of induction therapy (55 to 64 vs. ≥65 years), cytogenetic risk category at time of induction therapy (intermediate risk vs. poor risk) and received consolidation therapy following induction therapy (yes vs. no).
[2] Estimated with unstratified Cox proportional hazard model and log-rank test.

Source: Reviewer's analysis.

The data suggest that the treatment effect may vary by region (North America vs Europe vs other regions). Based on local clinical judgement, the standard treatment of US may be similar to that of Europe (EU) and may not be similar to that of Canada and Mexico. In other words, the pre-specified regions may not accurately reflect the different regional treatment practices. Additional analysis presented below compares the OS results between the US to EU.

On 24 June 2020 the Applicant responded to an Information Request sent by FDA on 9 June 2020. The Information Request inquired as to the possible difference in treatment effect by region. In their response, the Applicant stated that, "Notably the strategies and therapies used to treat patients with AML in the US and EU are very similar. In addition, there are relatively few

differences in the biological and clinical factors between US and EU patients that would lead to different outcomes for AML patients in terms of prognosis or response to treatment". The Applicant supported this statement with the following analyses which compared the US and EU subgroups:

- **Induction therapy.** Applicant conclusion: "Differences between the 2 regions were observed in the usage of idarubicin, daunorubicin, fludarabine, etoposide and mitoxantrone. However, these differences are expected to have no impact on the outcome of OS and RFS in Study CC-486-AML-001."
- **Response to induction therapy.** Applicant conclusion: "The proportion of subjects who had achieved CR at randomization was higher in the US. However, the same OS and RFS benefit was observed for subjects who achieved CRi in the US but with a smaller sample size."
- **Consolidation therapy.** Applicant conclusion: "The number of subjects who received consolidation therapy was similar between the US and EU (83.3% 50/60 for the US vs 79.9% 251/314 for the EU). A larger proportion of subjects in the EU received only 1 cycle of consolidation compared with US (49.4%; 155/314 for EU vs 35.0%; 21/60 for US). However, in the US, more subjects received 2 cycles of consolidation than in the EU (38.3%; 23/60 for US vs 29.0%; 91/314 for EU). There were also more US subject receiving 3 consolidation cycles than observed in the EU (10.0%; 6/60 for US vs 1.6%; 5/314 for EU)."

The Applicant noted that it is challenging to estimate the treatment effect in the US population based on the small observed sample size using conventional statistical methods. Consequently, the Applicant provided the following Bayesian Shrinkage estimations of treatment effects for OS and RFS respectively. The following model was specified:

$$\theta_g = \mu + \tau_g$$
$$\mu \sim N(0, B)$$
$$\tau_g \sim N(0, \omega^2)$$
$$\omega \sim \text{Half-Normal}(D)$$

Source: Equation 2 of the Applicant's response to the Information Request sent 9 June 2020.

In the model above, θ_g is the treatment effect for region *g*, μ is the overall treatment effect, and τ_g is the region-specific effect for region *g*. Note that this effect is specified as a random effect whose variance has a half-normal prior with standard deviation *D*. As *D* approaches infinity, the model converges to the usual fully stratified subgroup analysis. A *D* approaches 0, the effect of region-specific effects goes to 0, specifying a model where the treatment effect is identical across regions. The applicant specified *g=1,2* for the US and EU subgroups.

The results of the fully stratified analysis and the Bayesian shrinkage analyses with varying values of *D* are presented in Table 38. Note that the hazard ratio for the US in the fully stratified model is 0.90 (95% CI: 0.49, 1.66) compared to the hazard ratio for North America of 1.09 (0.65, 1.82)

(Table 37). Compared to hazard ratio estimation 0.90 (95% CI: 0.49, 1.66) using full stratified model, the treatment effect for US subgroup reduces to 0.84 (95% CI: 0.49, 1.61) with minimal shrinkage in the Bayesian model (*D*=100).

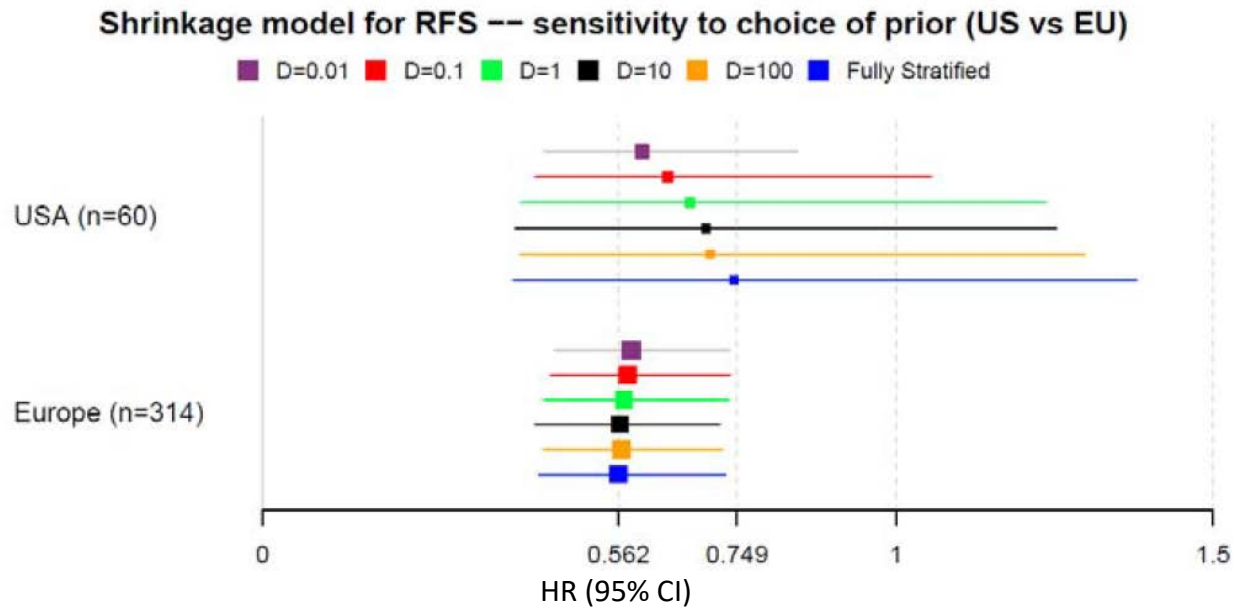
Table 38: CC-486-AML-001: Applicant Results for OS from Fully Stratified Subgroup Analysis and Shrinkage Model

	US **Hazard ratio (95% CI/CrI)**	**Europe** **Hazard ratio (95% CI/CrI)**
Fully Stratified Analysis	0.905 (0.492 , 1.659)	0.594 (0.455 , 0.775)
Shrinkage Model		
D = 100	0.841 (0.489 , 1.606)	0.605 (0.464 , 0.783)
D = 10	0.803 (0.435 , 1.472)	0.608 (0.444 , 0.835)
D = 1	0.807 (0.491 , 1.468)	0.611 (0.471 , 0.781)
D = 0.1	0.734 (0.478 , 1.280)	0.621 (0.479 , 0.800)
D = 0.01	0.664 (0.490 , 0.954)	0.631 (0.497 , 0.809)

CI = Confidence interval, CrI = credible interval;
[a] CI is provided for fully stratified analysis and CrI is provided for shrinkage model.

Source: Table 9 of the Applicant's response to the Information Request sent 9 June 2020.

Figure 19. CC-486-AML-001: Shrinkage Estimations for OS (US vs Europe)



Source: Figure 5 in the Applicant's Response to FDA Information Request on Page 22.

Statistical Reviewer's comment: The naïve estimates from subgroup analysis by region in Table 37 should be interpreted with caution for the US subgroup because of small sample size. The Applicant's Bayesian shrinkage analysis suggest that the hazard ratio for the treatment

effect in the US decreases with even minimal shrinkage. Note that this analysis does not include other regions, and therefore relies only on the assumption that the treatment effect is exchangeable between the US and EU. As these two regions comprise 83% of the trial population, including the other regions is not likely to have an appreciable effect on the results. In addition, including these regions would rely on the stronger assumption that the other regions (Asia, Australia, South America) have treatment effects that are exchangeable with those in the US and EU.

The reviewer additionally examined the difference between US and EU by multivariate Cox regression models. Table 39 presents such results with and without adjusting for other baseline characteristics.

Table 39. CC-486-AML-001: Multivariate Cox Regression Model for OS (US and EU Patients Only)

	Not Adjusted for Baseline Characteristics[1]		Adjust for Other Baseline Characteristics [2]	
Variable	**HR (95% CI)**	**P Value**	**HR (95% CI)**	**p-value**
Treatment (Oral AZA vs Placebo)	0.6 (0.46, 0.78)	0.0001	0.58 (0.44, 0.76)	0.0001
Region (US vs EU)	0.73 (0.45, 1.18)	0.2006	0.77 (0.48, 1.26)	0.3018
Treatment*Region (Oral AZA*US)	1.7 (0.87, 3.31)	0.12	1.8 (0.91, 3.55)	0.0889

[1]: Estimated with Cox proportional hazard model with covariates treatment, region and their interaction effect.
[2]: Estimated with Cox proportional hazard model with covariates treatment, region and their interaction effect, age at time of induction therapy (years), cytogenetic risk category at time of induction therapy (intermediate risk vs. poor risk), response firstly achieved after induction (CR vs. CRi), MRD status at baseline (positive vs. negative) and baseline ANC on logarithm scale.

Source: Reviewer's analysis.

Statistical Reviewer's comment: These results suggest that there is not enough evidence to conclude that efficacy differs significantly between the US and EU.

Efficacy Results – Exploratory and Other COA (PRO) Endpoints

Patient reported outcomes were not formally tested in Study CC-486-AML-001. However, the protocol specified Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale and the European quality of life-5 dimensions-3 levels (EQ-5D-3L) health utility index as secondary endpoints. In particular, a separate SAP for PROs specified that the associated endpoint to be the mean change from baseline HRQoL, as assessed by the FACIT-Fatigue Scale and EQ-5D, with a particular interest in assessing whether maintenance therapy with CC-486 causes clinically meaningful deterioration based on HRQoL data at different time points. No single primary analysis method was specified for this method. Rather, multiple methods were specified in the SAP, including descriptive analyses, repeated measures analyses, and time-to-event analyses. Only time-to-event analyses are summarized here.

(b) (4)

(b) (4)

Statistical Reviewer's comment: (b) (4)

FDA did not prospectively agree with the chosen thresholds for deterioration. In addition, FDA communicated that PRO endpoints would be considered exploratory on 5 Apr 2012.

(b) (4)

Additional Analyses Conducted on the Individual Trial

According to the CC-486-AML-001 study report, MRD status by flow cytometry was evaluated at screening. In response to IR dated 9 June 2020 (SDN 0018), MRD-negativity was defined as < 0.1% positive events in an assay with sensitivity "below 0.1%". Of 357 patients in the ITT population who had an FDA-adjudicated baseline status of CR, according to the applicant 180 were MRD-negative, and 171 were MRD-positive at screening. In a subset analysis of OS, the

treatment effect appeared to be consistent for patients who were either MRD-positive or MRD-negative and received oral azacitidine.

Table 40. CC-486-AML-001: OS Subgroup Analysis by MRD Status at Screening

MRD Status at Screening*	Oral azacitidine N	Placebo N	OS HR (95% CI)
• MRD-negative	96	84	0.78 (0.54, 1.12)
• MRD-positive	81	90	0.66 (0.47, 0.93)
• Unknown	1	5	-

Source: FDA Analysis
*Definitions of "MRD-negative" and "MRD-positive" are unvalidated

Clinical Reviewer's Comment: Survival is known to be affected by MRD status after induction. Although these results would be useful to healthcare providers to aid treatment decisions, the submission contained insufficient information to establish the analytical validity of the MRD assay performed (b) (4) ***as used in this study (see Section 4.3).*** (b) (4)

8.1.2. Additional Studies of the Activity of Oral Azacitidine in AML

There were three trials with data allowing for an assessment of efficacy of oral azacitidine for treatment of relapsed or refractory AML:

Study AZA-MDS-004

"A Phase 1, Multicenter, Open-label Study to Evaluate the Pharmacokinetics and Effect of Food of a New Tablet Formulation of Oral Azacitidine, and to Evaluate the Safety and Efficacy of Oral Azacitidine in Subjects with Myelodysplastic Syndromes, Chronic Myelomonocytic Leukemia or Acute Myeloid Leukemia"

Study AZA-MDS-004 was a multicenter, open-label, 3-part PK/PD study of oral azacitidine. Part 1 consisted of a randomized cross-over food effects study using azacitidine 300 mg daily x 3. Part 2 was a DDI study (omeprazole) using azacitidine 300 mg daily. Part 3 was an extension phase using azacitidine 300 mg daily on days 1-21 of each 28-day cycle until disease progression or unacceptable toxicity. Eligible patients were adults with MDS, CMML or AML. The primary endpoints of the study were the PK parameters. Safety and response endpoints were secondary. In the extension phase, safety evaluations were performed on Day 1 of each cycle (with laboratory testing weekly or biweekly Cycles 1-4). Marrow aspirate/biopsy samples during the extension phase were to be collected on Day 1 (± 7 days) of Cycles 3, 6, and 12 and every 6 months thereafter, and response was assessed by IWG criteria.

The first subject was enrolled on 2/9/2012, and the last subject completed on 5/12/2015. The accrual target was 36 patients; 34 subjects were enrolled, 32 were treated, and 31 entered the extension phase. The relevant safety data are discussed in Section 8.3. The study cohort included 9 patients with AML; one had primary refractory disease, 3 had relapsed disease, and 5 had prior treatment with HMAs for MDS prior to developing AML. They received a median of 1 (range, 1 - 9) cycles of azacitidine. The Applicant-assessed efficacy outcomes were 1 CR, 0 CRi and 0 PR for the 9 patients with AML. There was one investigator-assessed PR.

Study AZA-PH-US-2007-CL-005

"A Phase 1, Open-Label, Dose-Escalation Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Oral Azacitidine in Subjects With Myelodysplastic Syndromes (MDS), Chronic Myelomonocytic Leukemia (CMML) or Acute Myelogenous Leukemia (AML)"

Study AZA-PH-US-2007-CL-005 was a multicenter, open-label, 2-part dose-escalation study of oral azacitidine. Eligible patients were adults with MDS, CMML or AML (in the last amendment, enrollment was limited to patients with lower-risk MDS). Treatment in Part 1 consisted of SC azacitidine 75 mg/m^2 daily x 7 in Cycle 1, then oral azacitidine starting at 120 mg PO QD x 7 or a variety of doses and schedules in 28-day cycles. Part 2 evaluated escalating doses in various schedules. For tolerable dose levels, the cohort could be expanded to 20 or more patients (depending on the protocol version). Treatment could be continued until intolerable toxicity occurred. The primary endpoint was to determine the MTD of oral azacitidine. Additional PK and safety comparisons to SC azacitidine were planned, and hematologic response according to IWG was a secondary objective. The schedule of safety and efficacy monitoring tests varied by protocol amendment.

The first subject was enrolled on 9/6/2007, and the last subject completed on 7/30/2013. The accrual target was up to 150 patients; 131 subjects were enrolled, and 127 were treated with oral azacitidine. The relevant safety data are discussed in Section 8.3. The study participants received a median of 6 (range, 1 - 63) cycles of oral azacitidine. The study cohort included 23 patients with AML. The Applicant-assessed efficacy outcomes were 0 CR, 4 CRi and 0 PR among the patients with AML.

Study AZA-PH-US-2008-CL-008

"A Phase I, Open-Label, Dose-Ranging Study to Evaluate the Pharmacokinetics and Safety of Azacitidine Administered Subcutaneously and as Different Oral Formulations in Subjects with Myelodysplastic Syndromes (MDS), Chronic Myelomonocytic Leukemia (CMML), Acute Myelogenous Leukemia (AML), Lymphoma, and Multiple Myeloma"

Study AZA-PH-US-2008-CL-008 multicenter, open-label, 2-part PK study of various formulations of oral azacitidine. In Part 1, patients received SC azacitidine 75 mg/m^2 Days 1 and 15 in Cycle 1 and oral azacitidine on Days 3 and 5. In Part , patients received oral azacitidine: 600 mg daily on Days 1-7 of a 28-day cycle with crossover between fed and fasted conditions in Cycle 1 vs Cycle 2. In both parts, patients could continue on oral azacitidine in 28-day cycles thereafter. Eligible

patients were adults with hematologic malignancies. PK and safety comparisons to SC azacitidine were planned. Hematologic response was assessed by IWG prior to each odd numbered cycle and at end of study.

The first subject was enrolled on 8/12/2008, and the last subject completed on 4/6/2016. Thirty-one subjects were enrolled and treated. The relevant safety data are discussed in Section 8.3. The study cohort included 4 patients with AML. They received a median of 3 (range, 1 - 6) cycles of oral azacitidine. The Investigator-assessed efficacy outcomes were 3 CR for the patients with AML.

8.2 INTEGRATED REVIEW OF EFFECTIVENESS

8.2.1 Assessment of Efficacy Across Trials

Methods

The Applicant proposed the indication:

(b) (4)

The proposal was based on the results of Study CC-486-AML-001, a randomized Phase 3 trial of oral azacitidine vs placebo in patients in first CR or CRi after intensive induction with or without consolidation. OS was the primary endpoint. Two issues with the clinical development program were identified.

(b) (4)

(b) (4)

(b) (4)

The design of Study CC-486-AML-001 appears consistent with this intent and thus appropriate to support a marketing application.

Primary Endpoint

The primary endpoint of CC-486-AML-01 was overall survival as measured from randomization to death. Median OS was 24.7 months for the oral azacitidine arm vs 14.8 months in the placebo arm (HR 0.69 [95% CI: 0.55, 0.86], p = 0.0009).

Clinical TL Comments:

- ***OS is generally considered an acceptable measure of clinical benefit. In an era where additional effective therapies are prolonging survival, the OS endpoint may be affected by subsequent therapies. This does not appear to be a factor in this case.***
- ***OS may also be affected by differences in prognostic factors at baseline. Of the measured factors, there did not appear to be an imbalance between study arms.***
- ***MRD is one of the strongest factors affecting OS. The assay used in the trial lacked appropriate analytical validation, and as such MRD is an unmeasured factor for which bias has not been excluded.***
- ***The most challenging baseline factor to assess is the variability in prior therapy. This is discussed further in the subgroup analysis below.***
- ***The HR of 0.69 reflects approximately a 10-month difference in OS with a continued downward trend in survival. The meaningfulness of this effect will need to be balanced against toxicity.***

Secondary and Other Endpoints

The key secondary endpoint was relapse-free survival defined as time from randomization to relapse or death. Bone marrow aspirates were to be collected within 28 days of Day of Cycle 1 and during double-blind treatment phase on Day 1 (± 7 days) of Cycles 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, and the Treatment Discontinuation visit. After Cycle 36 bone marrow assessment for

disease relapse is performed only if clinically indicated. If disease relapse features are observed following a bone marrow aspirate, it was recommended that a repeat bone marrow aspirate be performed at least 3-4 weeks later to confirm disease relapse unless the blast count was greater than 50% in the marrow or peripheral blood. However, as discussed in 8.1.1, FDA defines RFS as the time from CR to relapse or death, and this trial enrolled a heterogeneous population with regard to disease status. In a subset analysis of 366 patients with FDA-adjudicated CR at baseline, patients treated with oral azacitidine had an RFS advantage with HR 0.66 (0.53, 0.84).

Clinical Reviewer's Comment: This analysis does not take into account the heterogeneity of the prior therapy (see discussion below) and the effects that might have on RFS. (b) (4)

Clinical TL Comment: Defining RFS as the time from randomization to relapse or death would have been acceptable in a study testing maintenance in only patients in CR following defined induction and consolidation. As CC-486-AML-01 is not a true maintenance design, RFS as proposed by the Applicant does not apply.

Other exploratory endpoints included use of FACIT-Fatigue, EQ-5D, and PINR scale to capture patient experience. FDA does not rely on EQ-5D as an assessment of overall quality of life and the PINR is an unvalidated scale (see OCE PFDD Review Memorandum, 8/12/20). For the FACIT-Fatigue scale, the applicant reported high completion rates "across all post-baseline visits" (b) (4)

Clinical Reviewer's Comment: Although the applicant reports a high completion rate of the FACIT-Fatigue tool, fewer than half of patients remained on the placebo arm beyond 6 cycles compared to almost 70% on the oral azacitidine arm. The high drop-out rate in placebo arm limits the interpretability of the between-arm comparison shown in Figure 20. Given the issues with the analysis of PROs in this study, the conclusions are not sufficient to support an efficacy claim (b) (4) ***The DCOA team elected not to comment on the validity of the FACIT-Fatigue scale as no validity or reliability information was provided in the submission (see DCOA Review Memorandum, 8/17/20).***

Subpopulations

Demographics: The analysis of OS by age identified no substantial issues (Appendix 15.5.1, Figure 28). There were too few Asian or Black patients to determine if efficacy differed by race. Of note was the substantial difference in OS HR between patients in North America (HR 1.09 (95% CI 0.65, 1.82)) or Europe (HR 0.6 (95% CI 0.46, 0.77) (Section 8.1.1, Table 35). As indicated in the review discussion in Section 8.1.1, however, based on the primary analysis, Bayesian shrinkage analyses and multivariate regression modeling, there was insufficient evidence to conclude that efficacy differs significantly between the US and Europe.

Baseline Disease Status: Patients who achieve only CRi are known to have poorer survival than

those who achieve CR. A subgroup analysis of OS by disease status after induction and at baseline is shown below. In both cases, the analysis for the CRi subset shows a wide confidence interval due to small patient numbers, but the point estimates are similar to those for patients in CR.

Table 41. CC-486-AML-001: Summary Subgroup Analysis of OS by Disease Status

	OS HR[1] (95% CI) by Disease Status	
	CR	**CRi**
By Induction Response	0.71 (0.55, 0.9)	0.74 (0.45, 1.2)
By FDA-Adjudicated Baseline Status	0.72 (0.56, 0.92)	0.87 (0.51, 1.5)

[1] Estimated with unstratified Cox proportional hazard model
Source: FDA Statistical Analysis Tables 24 and 25

Prior Consolidation: Standard intensive consolidation therapy for AML consists of 3 to 4 cycles of high dose cytarabine (see Section 2.1). In CC-486-AML-001, the majority of patients received fewer than recommended cycles of consolidation. Thirty-five percent received 2 cycles of consolidation, 45% received only one cycle, and 20% received no consolidation treatment after induction. A subgroup analysis of OS by number of consolidation cycles is shown below.

Table 42. CC-486-AML-001: Summary Subgroup Analysis of OS by Number of Consolidation Cycles

	HR by Cycles of Consolidation							
	None		**1**		**2**		**3**	
	Oral aza N = 52	Placebo N = 42	Oral aza N = 110	Placebo N = 102	Oral aza N = 70	Placebo N = 77	Oral aza N = 6	Placebo N = 13
OS HR[1] (95% CI)	0.55 (0.34, 0.89)		0.75 (0.55, 1.02)		0.69 (0.45, 1.04)		1.37 (0.37, 5.02)	

[1] Estimated with unstratified Cox proportional hazard model and log-rank test
Source: FDA Statistical Analysis Table 27

Clinical Reviewer's Comment: Patients who received 0 to 2 cycles of consolidation appear to benefit from treatment with oral azacitidine. However, for those who received no or minimal consolidation, potential underperformance of the placebo arm due to incomplete treatment for AML compared to oral azacitidine as a replacement for missing consolidation may have contributed to the magnitude of the observed treatment effect. For patients who completed 3 cycles of consolidation, no firm conclusions can be drawn regarding the efficacy of treatment with oral azacitidine due to the small patient numbers.

Baseline Minimal Residual Disease: As discussed in Section 8.1.1, in a subset analysis of OS in patients who were in CR at baseline, the treatment effect appeared to be consistent for patients who were either MRD-positive or MRD-negative at screening with HR 0.66 and 0.78, respectively, favoring the oral azacitidine arm (Table 30).

Clinical Reviewer's Comment: MRD status is an important factor affecting survival. However, the CDRH reviewer noted that the applicant used MRD assay results at a different limit of sensitivity than the assay that was originally analytically validated and that numerous modifications have been made to the original assay since validation (CDRH Consult Memorandum, 8/17/20). The current version of the assay used in the clinical trial has not been analytically validated. (b) (4)

Dose/Dose Response

Oral azacitidine for continued therapy in AML has been studied only at 300 mg QD x 14/28 days. The dose was selected on the basis of tolerability in patients being treated for MDS and AML (Study CC-486-AML-001 Clinical Study Report Section 9.4.4). Therefore, no data on efficacy by dose for continued treatment are available.

Additional Efficacy Considerations

The applicant provided efficacy data from 3 trials in patients with active AML treated with oral azacitidine at various doses/schedules (Table 29).

Table 43. Trials of Oral Azacitidine for Treatment of AML

	AZA-MDS-004 N = 9	**AZA-PH-US-2007-CL-005 N = 23**	**AZA-PH-US-2008-CL-008 N = 4**
AML Status	Unspecified	Unspecified	Relapsed/Refractory
Oral Azacitidine Dose Median cycles (range)	300 mg QD x 21/28 1 (1-9)	• 300 mg QD x 14/28 (n=4) 4 (1-8)	600 mg QD x 7/28 3 (1-6)
		• 400 mg BID x 14/28 (n=4) 4 (3-4)	
		• 300 mg QD x 21/28 (n=4) 1 (1-8)	
		• 400 mg BID x 21/28 (n=3) 5 (4-7)	
		• SC azacitidine x 7 days then oral azacitidine 120-480 mg QD x 7 (n=8) 5.5 (2-15)	
Investigator-assessed CR	1	0	3
Applicant-derived CR*	1	0	0

Source: FDA Analysis
* No data provided for confirmation of CR

Among 36 patients with active AML treated with oral azacitidine, 4 patients had an investigator-

assessed response of CR. No data were provided for adjudication of response, and the timing and duration of the responses were not described. One patient (3%) had an Applicant-assessed CR.

Clinical Reviewer's Comment: Based on the available data, oral azacitidine at the tested doses and schedules does not appear to be effective for induction of remission in AML.

8.2.2 Integrated Assessment of Effectiveness

The efficacy of post-induction oral azacitidine was established based on the results of the randomized, placebo-controlled pivotal study CC-486-AML-001 in which patients ≥ 55 years of age with AML in CR or CRi after intensive induction with or without consolidation had longer OS when treated with oral azacitidine compared with those who received placebo (HR 0.69 [95% CI: 0.55, 0.86], p = 0.0009). Although the overall trial was considered positive, the study design and heterogeneity of the study population enrolled in CC-486-AML-001 presented several challenges (b) (4)

- CC-486-AML-001 included patients who were in CR or CRi after induction and had no specific baseline requirement for patients to be in CR or CRi prior to the start of study therapy. Patients with AML who achieve responses less than CR after intensive induction are known to have poorer overall and relapse-free survival than those who achieve CR (Walter, 2010; Ovlisen, 2018). Randomization to CC-486-AML-001 was not stratified by post-induction response. After induction, 81% of the ITT population had achieved CR and 17% achieved CRi. At baseline, 78% were in CR and 17% were in CRi. Subset analyses of OS based on disease status at both time points showed wide confidence intervals for the CRi subsets due to small sample size, but similar point estimates for the hazard ratio compared to patients in CR.

- The eligibility criteria did not clearly describe an unfit patient population: adequate baseline organ function was required, 61% of patients were < 75 years old, and 92% had an ECOG status of 0-1. However, there was considerable variability in prior therapies received and many patients enrolled had not completed standard intensive consolidation therapy before randomization on CC-486-AML-001.

    - Only 19 patients (2%) enrolled on CC-486-AML-001 received 3 cycles of consolidation and none received 4 cycles. These patient numbers are too small to draw any conclusions regarding the efficacy of oral azacitidine in this subgroup.

    - Patients who received 0 to 2 cycles of consolidation appear to benefit from continued treatment with oral azacitidine compared to no further therapy.

- There may be a small number of patients in the study population who could have been

eligible for maintenance but given the trial design no conclusions can be drawn regarding the efficacy of oral azacitidine for maintenance therapy for AML.

The population accrued on CC-486-AML-001 was not consistent with the current understanding of the intent of AML CR1 maintenance. Given the trial design and the resulting heterogeneity of the study population, there are insufficient data to determine whether oral azacitidine could be an effective maintenance therapy for AML in CR1 or if the oral azacitidine arm outperformed placebo in an undertreated population. The study as designed, however, demonstrates a benefit with continued therapy and does address a substantial unmet need for additional treatments for patients who are unable to complete intensive curative therapy. (b) (4)

Although only patients ≥ 55 years of age were enrolled on CC-486-AML-001, given the mechanism of action of oral azacitidine, efficacy is expected to be similar across adults with AML and can be extrapolated to the full adult population.

8.3 REVIEW OF SAFETY

8.3.1. Safety Review Approach

FDA's review of safety included data from 472 patients enrolled on CC-486-AML-001 who received any treatment with oral azacitidine or placebo. Additional data from a subset of 36 patients enrolled on AZA-PH-US-2007-CL-005 who received oral azacitidine for treatment of hematologic malignancies at the same dose and schedule studied in CC-486-AML-001 were included for a side-by-side comparison. The safety population therefore was comprised of 505 patients (denoted in blue in Table 34). All safety analyses are based on the data provided in the 3-month safety update report ISS dataset (SDN 12).

Study AZA-MDS-003 was a randomized placebo-controlled trial in 290 patients with MDS treated at 300 mg x 21/28 (denoted in purple in Table 34). Given the randomized nature of the study and the fact that IV/SC azacitidine is indicated for treatment of patients with MDS, a brief analysis of safety in this study is described separately in Section 8.3.8.

The remaining trials included different patient populations, small numbers of patients, or patients treated at different doses and/or frequencies than the proposed USPI dosing. Safety in these trials is discussed briefly in Section 8.3.8.

Table 44. Safety Database – Studies of Oral Azacitidine Monotherapy by Dose and Disease

Dose x days/days per cycle	100 mg x 14/28	150 mg x14/28	200 mg x7/28	200 mg x14/28	300 mg x7/28	300 mg x14/28	Placebo	300 mg x21/28	Placebo	400 mg x14/28	400 mg x21/28	600 mg x7/28
Continued Therapy or Maintenance												
CC-486-AML-001* (Pivotal trial)						236	233					
CC-486-AML-002 • AML post HSCT • MDS post HSCT		4 0	2 1	16 3	4 0							
Treatment (total)	**2**					**36**		**181**	**109**	**6**	**6**	**14**
MDS (total)						29		164		2	3	14
•AZA-MDS-003*								107	109			
•AZA-MDS-004								18				
•AZA-MDS-005								5				
•AZA-PH-US-2007-CL-005						29		34		2	3	
•AZA-PH-US-2008-CL-008												14
•CC-486-MDS-001	2											
AML (total)						4		13		4	3	4
• AZA-MDS-004								9				
• AZA-PH-US-2007-CL-005 • AZA-PH-US-2008-CL-008						4		4		4	3	4
CMML (total)						3		4				
• AZA-MDS-004								4				
• AZA-PH-US-2007-CL-005						3						

*Randomized, placebo-controlled trials
Source: FDA Analysis

8.3.2. Review of the Safety Database

Overall Exposure

Table 45. Safety Population – Exposure

	Continued Therapy CC-486-AML-001		Treatment of Active Disease
	Oral azacitidine N = 236	Placebo N = 233	AZA-PH-US-2007-CL-005 N = 36
Treatment duration (months)	11.6	5.8	7.7
Median (range)	(0.5, 77.1)	(0.7, 71.4)	(0.9, 46.3)
Average Daily Dose^ (mg)	300	300	300
Median (range)	(202.8, 300.6)	(150, 353.6)	(142.3, 305.7)
Number of Cycles	12	6	7
Median (range)	(1-82)	(1-76)	(1, 49)
• **1+**	100%	100%	100%
• **2+**	94%	93%	97%
• **3+**	86%	84%	92%
• **4+**	83%	73%	81%
• **5+**	79%	66%	78%
• **6+**	74%	58%	75%
• **12+**	53%	32%	22%
• **24+**	31%	15%	11%

Source: FDA Analysis ^ Total cumulative dose/# of days dosed

Clinical Reviewer's Comment: Given the sharp drop-off in patients remaining on the placebo arm beyond Cycle 5-6, a between-arm comparison of safety across the all cycles is likely to artificially skew the safety profile against the investigational arm. Therefore, major safety analyses will be presented both across all cycles and restricted to Cycles 1-5 for a more balanced comparison.

Key characteristics of the safety population are shown below.

Table 46. Safety Population – Key Characteristics

	Continued Therapy CC-486-AML-001		**Treatment of Active Disease AZA-PH-US-2007-CL-005 N = 36**
	Oral azacitidine N = 236	**Placebo N = 233**	
Age (years) Median (range)	68 (55-86)	68 (55-82)	72 (51-85)
Age group • 50 - < 65 years • ≥ 65 - < 75 years • ≥ 75 years	 65 (28%) 143 (61%) 28 (12%)	 68 (29%) 142 (61%) 23 (10%)	 8 (22%) 18 (50%) 10 (28%)
Gender • Female • Male	 118 (50%) 118 (50%)	 106 (45%) 127 (55%)	 11 (31%) 25 (69%)
Race • White • Asian • Black/Other • Unknown	 215 (91%) 6 (3%) 13 (6%) 2 (1%)	 197 (85%) 20 (9%) 16 (7%) 0	 34 (94%) - 2 (6%) -
Diagnosis • AML • MDS • CMML	 236 (100%) - -	 233 (100%) - -	 4 (11%) 29 (81%) 3 (8%)

Source: FDA Analysis

Adequacy of the Safety Database

The database includes over 200 patients treated with at least one dose of post-induction oral azacitidine. A comparable number of patients are in the placebo-controlled arm for comparison. Safety data for an additional 36 patients with hematologic malignancies treated at the same/dose and schedule for active disease are available for context.

Clinical Reviewer's Comment: The size of the database is adequate to assess for clinically-important adverse reactions that occur at a low frequency.

The age range in the database is largely limited to patients ≥ 55 years old (the active disease cohort includes 4 patients between 50 and 55 years old). Although this reflects a large proportion of the at-risk population, it is probable that younger, less fit patients who are unable to continue intensive therapy might also benefit from continued treatment with oral azacitidine. However, azacitidine IV/SC has a well-established safety profile across age groups. Also, the ISS dataset includes 3 patients with AML and 12 patients with MDS treated with oral azacitidine monotherapy at various dose levels/schedules. Assuming no major differences in the Safety Population subset analysis by age group and no unique safety findings in the younger patients from the ISS dataset, safety in a younger adult population may be extrapolated from the Safety Population. No safety data are available for pediatric patients. Overall, the data submitted are adequate to assess the safety of oral azacitidine in the intended population.

8.3.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data for the ISS were provided in CDISC data files. No major issues involving data integrity or submission quality were identified.

Categorization of Adverse Events

Adverse events were reported down to the verbatim term and were coded using MedDRA 22.0. CTCAE Version 4.0 was used for toxicity grading. Treatment-emergent adverse events (TEAE) excluded events starting and ending before the start of study drug. FDA administered custom queries for selected adverse events of special interest (see Appendix 15.6 for FDA's grouped terms).

Routine Clinical Tests

Routine clinical tests included vital signs, CBC and serum chemistry laboratory analysis. See 8.1.1 for a description of the frequency of clinical assessments. The frequency of clinical assessments is considered adequate to assess the risks of serious safety signals.

8.3.4. Safety Results

Deaths

A total of 329 deaths were reported on CC-486-AML-001 and 5 deaths were reported in AZA-PH-2007-CL-005.

Table 47. Safety Population – Deaths

	Continued Therapy CC-486-AML-001		Treatment of Active Disease AZA-PH-US-2007-CL-005 N = 36
	Oral azacitidine N = 236	Placebo N = 233	
Deaths (total)	158 (67%)	171 (73%)	5 (14%)
30-Day mortality	1 (< 1%)	0	0
On-treatment deaths^	14 (6%)	12 (5%)	3 (8%)
• **Adverse Event**	9 (4%)	3 (1%)	3 (8%)
• **Sepsis/infection**	5 (2%)	0	1 (3%)
• **Cerebral hemorrhage**	2 (1%)	1 (< 1%)	0
• **Other**	2 (1%)	2 (1%)	2 (6%)
• **Disease**	5 (2%)	9 (4%)	0

Source: FDA Analysis
^Deaths within 28 days of end of treatment

On-treatment deaths in AZA-PH-US-2007-CL-005 were due to pneumonia/septic shock in 2 patients with MDS and ischemic bowel in the setting of AML. Causes of death (COD) of on-treatment deaths in the oral azacitidine arm of CC-486-AML-001 were reported as AML (5), sepsis/infection (5), CNS hemorrhage (2), cardiogenic shock (1), and suicide (1).

FDA adjudicated all treatment-emergent deaths occurring within 28 days of end of treatment (EOT) and agreed with the investigators' assessments in most cases. For CC-486-AML-001, all deaths in the placebo arm occurred in the setting of disease. In the oral azacitidine arm, 5 deaths due to AR occurred in the setting of documented active disease, 1 subject had an intracranial hemorrhage while on rivaroxaban for infarct/atrial fibrillation prophylaxis (platelets ~50 Gi/L), 1 subject had discontinued treatment due to metastatic lung carcinoma with intraspinal extension and died of cardiogenic shock, and 1 subject committed suicide.

However, FDA disagreed with one death in the oral azacitidine arm which the applicant reported as a death due to AML. Patient (b) (6) was a 59-year-old female who had achieved CR after induction and received no consolidation. A timeline of events from the narrative is presented below.

Cycle/Date (if given)	Bone marrow blasts	Peripheral blasts	Notes
Cycle 9 – (b) (6)	10%	1%	Relapse
Cycle 9 – 5/8/17	16.5%		Blast persistence + relapse

Cycle/Date (if given)	Bone marrow blasts	Peripheral blasts	Notes
Cycle 12 – (b) (6)	14%	1%	Blast persistence – "At start of Cycle 12 schedule of study treatment was increased to 21 days due to AML relapse/progression."
Cycle 21 – (b) (6)	5%		
Cycle 24 – (b) (6)	4%	0%	"In keeping with reactive changes under treatment"
Cycle 26			Hospitalized for Grade 3 viral enteritis – pip/tazo
Cycle 28			Grade 2 skin infection - cephalexin
Cycle 31 – (b) (6)	5%		"In keeping with reactive changes under treatment"
Cycle 32 – (b) (6)			Began to experience fevers Initiated prednisolone for ongoing neutrophilic dermatosis (through end of C33) Grade 3 febrile neutropenia (ANC 900) – cultures negative; pip/tazo, ceftriaxone, bactrim Rechallenged with study drug – "negative"
Cycle 33 – (b) (6)	4.5%	0%	"In keeping with reactive changes under treatment"
Cycle 34 – (b) (6)			Grade 3 Sweet's syndrome – prednisolone, resolved
Cycle 35 – (b) (6)			Grade 2 cellulitis – prednisolone, resolved
Cycle 36 – (b) (6)			Grade 2 non-serious skin infection - Augmentin
Cycle 37 – (b) (6)			Grade 2 non-serious diarrhea – loperamide (b) (6) – prednisolone for skin infection (b) (6) – hospitalized for Grade 4 colitis, fecal incontinence • CT – severe pancolitis, Colonoscopy - ulcers • PE – erythema/excoriation/raised lesions previously dx as Sweet's • WBC 28, ANC 21.5 (Gi/L? no units), CRP 381 • C. diff positive (b) (6) – died of septic shock

Source: FDA Analysis

As noted multiple times throughout the narrative and in the conclusion, this patient had blasts ≤ 5% "in keeping with reactive changes under treatment." Sweet syndrome has multiple

potential causes including drugs like Bactrim and Vidaza. Although there may have been other contributing factors to her colitis including antibiotics and steroids, this does not rule out a potential contribution from oral azacitidine and there is no compelling evidence that active AML contributed to her death. Therefore, FDA considers this death at least possibly related to oral azacitidine.

Serious Adverse Events

On-treatment (occurring within 28 days of the last dose of therapy) SAEs are shown in the table below by SOC in decreasing order of incidence in the oral azacitidine arm of CC-486-AML-001.

Table 48. Safety Population – On-treatment Serious Adverse Events by SOC

	Continued Therapy CC-486-AML-001		Treatment of Active Disease AZA-PH-US-2007-CL-005 N = 36
	Oral Aza N = 236	Placebo N = 233	
At least 1 serious TEAE	33%	26%	53%
Infections and Infestations	19%	30%	0%
Blood and lymphatic system disorders	9%	7%	14%
Gastrointestinal disorders	6%	3%	19%
General disorders and administration site conditions	4%	3%	6%
Cardiac disorders	3%	2%	6%
Injury, poisoning, procedural complications	3%	1%	6%
Respiratory, thoracic, and mediastinal disorders	3%	2%	6%
Metabolism and nutrition disorders	3%	1%	6%

Source: FDA Analysis

SAEs occurring in > 2% of patients in the oral azacitidine arm of CC-486-AML-001 were pneumonia (8%) and febrile neutropenia (7%).

Dropouts and/or Discontinuations Due to Adverse Effects

TEAEs requiring discontinuation or dose reduction in at least 1% of patients are shown below.

Table 49. Safety Population – TEAEs Leading Dose Discontinuation or Reduction

	Continued Therapy CC-486-AML-001		Treatment of Active Disease AZA-PH-US-2007-CL-005 N = 36
	Oral aza N = 236	Placebo N = 233	
Treatment Discontinuation	18 (8%)	3 (1%)	6 (17%)
• Nausea	5 (2%)	0	0
• Diarrhea	4 (2%)	0	0
• Vomiting	3 (1%)	0	0
• Abdominal pain	2 (1%)	0	0
• Fatigue [a]	2 (1%)	0	0
• Pneumonia [a]	2 (1%)	0	2 (6%)
• Thrombocytopenia	0	2 (1%)	0
Dose Reduction	32 (14%)	4 (2%)	2 (6%)
• Neutropenia	13 (6%)	0	1 (3%)
• Diarrhea	8 (4%)	0	1 (3%)
• Nausea	4 (2%)	0	0
• Thrombocytopenia	4 (2%)	3 (1%)	0
• Leukopenia	2 (1%)	1 (<1%)	1 (3%)
• Vomiting	2 (1%)	0	0
• Fatigue [a]	2 (1%)	0	0
• Pneumonia [a]	2 (1%)	0	0

Source: FDA Analysis
[a] Grouped term

In patients who received oral azacitidine, discontinuation, dose reduction, and dose interruption were predominantly due to GI toxicities or cytopenias. In the oral azacitidine arm of CC-486-AML-001, GI toxicities led to permanent discontinuation, dose reduction, and dose interruption in 5%, 5%, and 13% of patients, respectively. Cytopenias led to dose reduction in 8% and dose interruption in 27% of patients.

Treatment Emergent Adverse Events

Table 50. Safety Population – Common (≥ 10%) On-treatment TEAEs in Patients Treated with Oral Azacitidine with ≥ 2% Difference Compared to Placebo – Any Cycle

	Continued Therapy CC-486-AML-001				Treatment of Active Disease AZA-PH-US-2007-CL-005 N = 36	
	Oral Aza N = 236		Placebo N = 233			
	All Grade	Grade ≥ 3	All Grade	Grade ≥ 3	All Grade	Grade ≥ 3
Nausea	65%	3%	24%	<1%	67%	3%
Vomiting	60%	3%	10%	0%	47%	8%
Diarrhea	50%	5%	21%	1%	83%	6%
Fatigue [a]	44%	4%	25%	1%	56%	3%
Constipation	39%	1%	24%	0%	61%	0%
Pneumonia [a]	27%	9%	17%	5%	31%	19%
Abdominal pain [a]	22%	2%	13%	<1%	44%	0%
Arthralgia	14%	1%	10%	<1%	14%	3%
Decreased appetite	13%	1%	6%	1%	28%	0%
Back pain	12%	1%	10%	1%	14%	3%
Febrile neutropenia	12%	11%	8%	8%	6%	6%
Dizziness	11%	0%	9%	0%	31%	0%
Pain in extremity	11%	<1%	5%	0%	14%	0%

Source: FDA Analysis
[a] Grouped term

However, as noted in Table 35, the number of patients remaining on the placebo arm drops off considerably after Cycle 5 making the comparison of AEs between arms over the full study less accurate. A comparison of on-treatment TEAEs restricted to Cycles 1-5 is presented below.

Table 51. Safety Population – Common (≥ 10%) On-treatment TEAEs in Patients Treated with Oral Azacitidine with ≥ 2% Difference Compared to Placebo – Cycles 1-5

	Continued Therapy CC-486-AML-001				Treatment of Active Disease AZA-PH-US-2007-CL-005	
	Oral Aza N = 236		Placebo N = 233		N = 36	
	All Grade	Grade ≥ 3	All Grade	Grade ≥ 3	All Grade	Grade ≥ 3
Any	96%	56%	93%	54%	100%	61%
Nausea	58%	2%	19%	< 1%	64%	3%
Vomiting	54%	3%	7%	0%	44%	8%
Diarrhea	38%	3%	14%	1%	75%	6%
Constipation	31%	< 1%	21%	0%	61%	0%
Fatigue [a]	30%	2%	19%	1%	50%	3%
Abdominal pain [a]	14%	1%	10%	< 1%	31%	0%

Source: FDA Analysis
[a] Grouped term

Clinical Reviewer's Comment: The major class of adverse reactions related to treatment with oral azacitidine is gastrointestinal disorders. Patients in the oral azacitidine arm also had an increased incidence of low-grade fatigue compared to those who received placebo.

In the contrast to the analysis of TEAEs across all cycles, when the analysis was restricted to the 1st 5 cycles in CC-486-AML-001:

- ***Pneumonia occurred in 9% of patients in the oral azacitidine arm vs 9% in the placebo arm (and 25% in the active disease cohort).***
- ***Febrile neutropenia was reported in 3% vs 5% of patients in the oral azacitidine and placebo arms, respectively.***

There were no AE preferred terms reported in the Continued Therapy trial that were not reported in the treatment cohort. Among all patients who received oral azacitidine, with the exception of all grade vomiting, both all-grade and Grade ≥ 3 TEAEs occurred at a higher rate in the treatment cohort than in the oral azacitidine Continued Therapy cohort. Given these findings, the remainder of the safety analysis will focus on data from CC-486-AML-001.

Adverse Events of Special Interest

Gastrointestinal Toxicity

GI toxicities are expected with oral therapeutics. An analysis of the ADCM data file for antiemetic and antidiarrheal use where the indication (CMINDC) was recorded as adverse event, emesis, diarrhea, or treatment and prophylaxis is presented below.

Table 52. CC-486-AML-001 – Antiemetic Use for Treatment of Adverse Reaction (Cycles 1-5)

	Oral Azacitidine		Placebo	
Cycle 1	75/236	32%	12/233	5%
Cycle 2	21/222	9%	4/217	2%
Cycle 3	13/204	6%	2/195	1%
Cycle 4	12/196	6%	0	-
Cycle 5	13/186	7%	3/154	2%

Source: FDA Analysis

Table 53. CC-486-AML-001 – Antidiarrheal Use for Treatment of Adverse Reaction (Cycles 1-5)

	Oral Azacitidine		Placebo	
Cycle 1	24/236	10%	0	-
Cycle 2	10/222	5%	4/217	2%
Cycle 3	3/204	1%	3/195	2%
Cycle 4	7/196	4%	5/169	3%
Cycle 5	5/186	3%	2/154	1%

Source: FDA Analysis

[a] Treatment – CMINDC ≈ diarrhea, treatment and prophylaxis

Clinical Reviewer's Comment: As shown in the previous section, increased GI toxicities were the major safety finding seen with treatment with oral azacitidine. Antiemetic prophylaxis was required per protocol but could be omitted for patients without nausea/vomiting during the first two cycles. Table 18 in Section 8.1.1 shows prophylactic antiemetic use in Cycles 1-5. The highest incidence of antiemetic use for treatment of nausea/vomiting occurred during the first cycle and decreased with subsequent cycles (Table 42). Antidiarrheal use for treatment of diarrhea also decreased with subsequent cycles (Table 43).

Overall, GI toxicities were typically low grade and occurred most often during the first few cycles of treatment. Nausea and vomiting appeared to be manageable with antiemetic prophylaxis. Fewer than 10% of patients required treatment for a GI toxicity after the 1st cycle.

Myelosuppression

Table 54. CC-486-AML-001 – Selected Hematologic Laboratory Shifts in Subjects with Baseline Grade ≤ 2

Laboratory Abnormality	Oral Azacitidine			Placebo		
	Baseline Grade ≤ 2	Grade ≥ 3 at least once on tx		Baseline Grade ≤ 2	Grade ≥ 3 at least once on tx	
	n	n	%	n	n	%
Any Cycle						
• Neutropenia	227	146	64%	225	108	48%
• Leukopenia	231	124	54%	228	74	32%
• Thrombocytopenia	227	79	35%	219	72	33%
• Anemia	235	27	11%	231	14	6%
Cycle 1-5						
• Neutropenia	227	101	44%	225	61	27%
• Leukopenia	231	78	34%	228	39	17%
• Thrombocytopenia	227	43	19%	219	26	12%
• Anemia	235	9	4%	231	8	3%

Source: FDA Analysis

Neutropenia and thrombocytopenia were notably increased in patients treated with oral azacitidine with a majority of events occurring during the 1st 5 cycles.

Clinical Reviewer's Comment: Cytopenias are anticipated toxicities when treating with cytotoxic drugs. Treatment-emergent Grade 3-4 neutropenia and thrombocytopenia were higher in the oral azacitidine arm compared to the placebo arm, as expected. However, some Grade 3-4 shifts were also noted in the placebo arm. In a response to IR, the Applicant provided the analyses below excluding hematologic abnormalities occurring in the setting of relapse.

Table 55. CC-486-AML-001 – Selected Hematologic Laboratory Abnormalities Excluding Relapse

	Oral Azacitidine		Placebo	
	Baseline Grade 0-2 N	Post-Baseline Grade 3 or 4 n (%)	Baseline Grade 0-2 N	Post-Baseline Grade 3 or 4 n (%)
All Cycles				
• Neutropenia	223	109 (49)	217	50 (23)
• Thrombocytopenia	222	46 (21)	212	22 (10)
• Anemia	229	10 (4)	223	7 (3)
Cycles 1-5				
• Neutropenia	223	90 (40)	217	42 (19)
• Thrombocytopenia	222	36 (16)	212	15 (7)
• Anemia	229	6 (3)	223	5 (2)

Source: Adapted from Applicant Response to Package Insert Draft IR, SDN 0025, Table 14.3.4.2.1.fda3

Although the incidences of neutropenia and thrombocytopenia excluding relapse are lower than those in Table 44, a background level of Grade 3-4 treatment-emergent shifts is still observed in the placebo arm.

Laboratory Findings

Table 56. CC-486-AML-001 – Nonhematologic Laboratory Shifts in Subjects with Baseline Grade ≤ 2 – Any Cycle

	Oral Azacitidine			Placebo		
Laboratory Abnormality	**Baseline Grade ≤ 2**	**Grade ≥ 3 at least once on tx**		**Baseline Grade ≤ 2**	**Grade ≥ 3 at least once on tx**	
	n	**n**	**%**	**n**	**n**	**%**
Hepatic toxicity						
• ALT increased	236	5	2%	233	4	2%
• Hyperbilirubinemia	236	1	< 1%	233	0	0%
• AST increased	234	0	0%	233	4	2%
Other						
• Hyperuricemia	215	38	18%	220	33	15%
• Hyperglycemia	228	9	4%	227	13	6%
• Hypokalemia	235	8	3%	231	8	3%
• Hypophosphatemia	236	7	3%	232	7	3%
• Hyponatremia	235	6	3%	233	3	1%
• Hypoalbuminemia	236	3	1%	233	0	0%
• Alk phos elevated	236	2	1%	233	0	0%
• Hypocalcemia	235	2	1%	233	1	< 1%
• Hyperkalemia	236	1	< 1%	233	2	1%
• Hypoglycemia	236	-	-	233	-	-
• Hypercalcemia	236	-	-	233	-	-
• Creatinine elevated	236	-	-	233	-	-
• Hypernatremia	236	-	-	233	-	-

Source: FDA Analysis

Table 57. CC-486-AML-001 – Nonhematologic Laboratory Shifts in Subjects with Baseline Grade ≤ 2 – Cycles 1-5

Laboratory Abnormality	Oral Azacitidine			Placebo		
	Baseline Grade ≤ 2	Grade ≥ 3 at least once on tx		Baseline Grade ≤ 2	Grade ≥ 3 at least once on tx	
	n	n	%	n	n	%
Hepatic toxicity						
• ALT increased	236	1	< 1%	233	2	1%
• Hyperbilirubinemia	236	-	-	233	3	1%
• AST increased	234	-	-	233	-	-
Other						
• Hyperuricemia	215	23	11%	220	16	7%
• Hyperglycemia	228	2	1%	227	5	2%
• Hypokalemia	235	2	1%	231	2	1%
• Hypophosphatemia	236	2	1%	232	1	< 1%
• Hyponatremia	235	3	5%	233	1	< 1%

Source: FDA Analysis
ADLB VISIT = C1-5 or unscheduled w/in D140

Except for hyperuricemia, possibly in the setting of relapse, the incidence of all other treatment-emergent Grade 3 or 4 laboratory abnormalities was ≤ 10% and was similar between treatment arms. No significant shifts in hepatic or renal laboratory values were reported.

Vital Signs

Vital signs were assessed on Day 1 of each cycle. The applicant did not identify any unexpected trends or clinically meaningful post-baseline findings in vital sign parameters.

QT/Electrocardiograms (ECGs)

- There were no reported events of electrocardiogram QT prolonged.
- One patient in the oral azacitidine died of cardiogenic shock and no patients in the placebo group had a fatal cardiac AE.
- Grade 3 or 4 cardiac AEs reported for at least 2 subjects in the oral azacitidine arm: syncope (2% vs <1%) and atrial fibrillation (2% vs 0%)
- Cardiac AESI of any grade occurred in 20% of patients in the oral azacitidine arm vs 17% in the placebo arm. Events were mostly Grade 1 or 2 in severity.
- The only cardiac AESI (any grade) which occurred in > 5% of subjects in the oral azacitidine arm was peripheral edema (9% vs 10%)

Immunogenicity

No immunogenicity data were submitted.

8.3.5 Analysis of Submission-Specific Safety Issues

See discussion of AESI above.

8.3.6 Safety Analyses by Demographic Subgroups

TEAEs by Sex

There were no notable differences in TEAEs between male and female subjects within treatment groups.

TEAEs by Age

Table 58. CC-486-AML-001 – Common (≥ 10%) All Grade TEAEs by Age Group – Cycles 1-5

	Age < 65 years		Age ≥ 65 - < 75 years		Age > 75 years	
	Oral Azacitidine N = 65	Placebo N = 68	Oral Azacitidine N = 143	Placebo N = 142	Oral Azacitidine N = 28	Placebo N = 23
Nausea	57%	25%	59%	17%	50%	4%
Vomiting	54%	7%	55%	7%	57%	4%
Diarrhea	42%	16%	34%	12%	46%	17%
Fatigue [a]	23%	13%	29%	15%	46%	22%
Constipation	31%	24%	29%	19%	46%	30%
Pneumonia [a]	14%	9%	7%	11%	7%	4%
Abdominal pain [a]	9%	10%	15%	10%	18%	13%
Arthralgia	11%	4%	8%	9%	7%	0%
Decreased appetite	9%	4%	5%	4%	18%	0%

Source: FDA Analysis
[a] Grouped term

Patients in the ≥ 75 years age group had a higher incidence of low-grade fatigue, constipation, and decreased appetite than other age groups, but the data are limited by the small number of patients in this age group. As with the overall safety population, the incidence of Grade ≥ 3 TEAEs was low in both arms (not shown) and there were no notable differences by age group.

Among 15 patients with active AML or MDS ages 30-53 years treated with a median of 4 cycles (Range 1-13) of oral azacitidine at doses of 300-400mg x 14/28 or 21/28 days, no new AEs were

observed. TEAEs reported in more than 2 patients were GI toxicities, pneumonia, fatigue, and cough. No Grade ≥ 3 AEs were reported in more than 2 patients.

TEAEs by Race
More than 95% of patients in all racial groups experienced at least 1 TEAE. However, given the small number of patients treated with oral azacitidine in the Asian (6) and Black/Other (13) groups, no comparisons can be made.

Clinical Reviewer's Comment: The numbers by race are limited, but overall the safety review by demographic subgroup does not indicate any safety signal that warrants a limitation of use or warning.

8.3.7 Clinical Outcomes Assessments Informing Tolerability/Safety

Health-related quality of life was assessed using the Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue scale v.4 and the European Quality of Life–Five Dimensions–Three Levels (EQ-5D-3L) questionnaire, and the Physical Impairment Numeric Rating (PINR) scale. The Applicant reported that compliance rates remained high (>85%) until the EOT assessment and (b) (4) in overall fatigue observed between the two study arms.

Clinical Reviewer's Comment: Reports (b) (4) ***in overall fatigue could contribute information to the overall safety analysis. However, although the applicant reported a high compliance rate, the validity of a between-arm comparison over the trial is questionable given the high drop-out rate in the placebo arm (see Table 35). Also, the EQ-5D is not an acceptable tool for assessment of overall HRQL and the PINR scale is not validated (OCE PFDD Memorandum, 8/12/20). Finally, all PRO endpoints were exploratory (communicated to the applicant April 12, 2012 and at subsequent SPA-related meetings).*** (b) (4)

8.3.8 Specific Safety Studies/Clinical Trials (including dose-related safety)

No studies were conducted to evaluate a specific safety concern.

AZA-MDS-003 (NCT01566695) was a randomized trial of best supportive care plus oral azacitidine or placebo for IPSS lower-risk MDS with RBC transfusion-dependent anemia and thrombocytopenia. Per protocol, the planned enrollment was 386 patients. Ultimately, 216 patients were randomized to treatment with oral azacitidine (n = 107) or placebo (n = 109). One-hundred and seven patients received a median of 5 cycles of oral azacitidine 300 mg daily for 21 days of a 28-day cycle.

The trial was placed on partial clinical hold due to an imbalance in early mortality. No

imbalance in baseline demographics, disease characteristics, and medical history between arms was identified indicating that the disparity in deaths was drug-related. On-treatment deaths due to AE occurred in 22% of patients in the oral azacitidine arm compared with 7% in the placebo arm. There was a significant imbalance in fatal infections occurring during Cycles 1-3 (12% vs 2%). Overall TEAEs and serious, Grade 3-4, and fatal TEAEs were all higher in the oral azacitidine arm as were TEAEs requiring dose reduction or interruption. The highest incidence of TEAEs occurred in Cycles 1 and 2.

The partial clinical hold was lifted after the addition of safety measures including reduction of dosing from 300 mg QD x 21/28 to 14/28 for the first 2 cycles and increased monitoring, but enrollment to the study was never re-opened.

Clinical Reviewer's Comment: This clinically significant safety signal merits a warning in the USPI for increased mortality in patients with MDS treated with oral azacitidine to advise clinicians that treatment in this unapproved population is not recommended outside of clinical trials.

Other studies in the safety database

Across the five dose-finding studies in active hematologic malignancies, there were no new safety signals identified. Although the number of patients treated at each dose level was too small to draw conclusions regarding dose-related safety, the most common ARs seen at most dose levels were GI toxicities, fatigue, and cytopenia preferred terms. Common (> 10%) Grade ≥ 3 ARs were limited to febrile neutropenia and fatigue.

CC-486-AML-002 was a dose-finding trial in patients with hematologic malignancies who were postHSCT. Again, the common ARs were GI toxicities and fatigue. Gut GVHD was reported in 6 patients (across 2 dose levels). Grade ≥ 3 ARs occurring in more than 2 patients at any dose level were nausea and diarrhea.

Across the solid tumor trials, in patients who received oral azacitidine monotherapy (nasopharyngeal carcinoma) common (> 10%) ARs were GI toxicities, fatigue, cough, dysphagia, and weight decreased. The remainder of the data were from patients treated with oral azacitidine plus other drugs. Common ARs in this population were similar with the addition of alopecia, back pain, dyspnea, and peripheral edema. No new Grade ≥ 3 ARs were reported in either study.

Clinical Reviewer's Comment: There were no new safety signals in other studies in the safety database that could not be attributed to the patient population (e.g. gut GVHD in the postHSCT population) or concomitant therapy (e.g. alopecia in solid tumor patients treated with combination therapy including carboplatin or nabpaclitaxel).

8.3.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No nonclinical carcinogenicity studies were undertaken.

Human Reproduction and Pregnancy

Based on the mechanism of action and findings in animals, oral azacitidine can cause fetal harm when administered to pregnant women. A warning for embryofetal toxicity should be included in the USPI.

Pediatrics and Assessment of Effects on Growth

The applicant has Orphan Designation for azacitidine for the treatment of patients with acute myeloid leukemia and is therefore exempt from pediatric studies under the Pediatric Research Equity Act (PREA). No pediatric data were submitted with the application.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The applicant did not provide any reported cases of overdose of oral azacitidine in the AML population. Oral azacitidine does not have abuse potential.

8.3.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Interstitial lung disease, tumor lysis syndrome, Sweet's syndrome (acute febrile neutrophilic dermatosis), necrotizing fasciitis (including fatal cases), and differentiation syndrome were identified as safety concerns in the postmarketing experience for IV/SC azacitidine and are included in the Vidaza USPI.

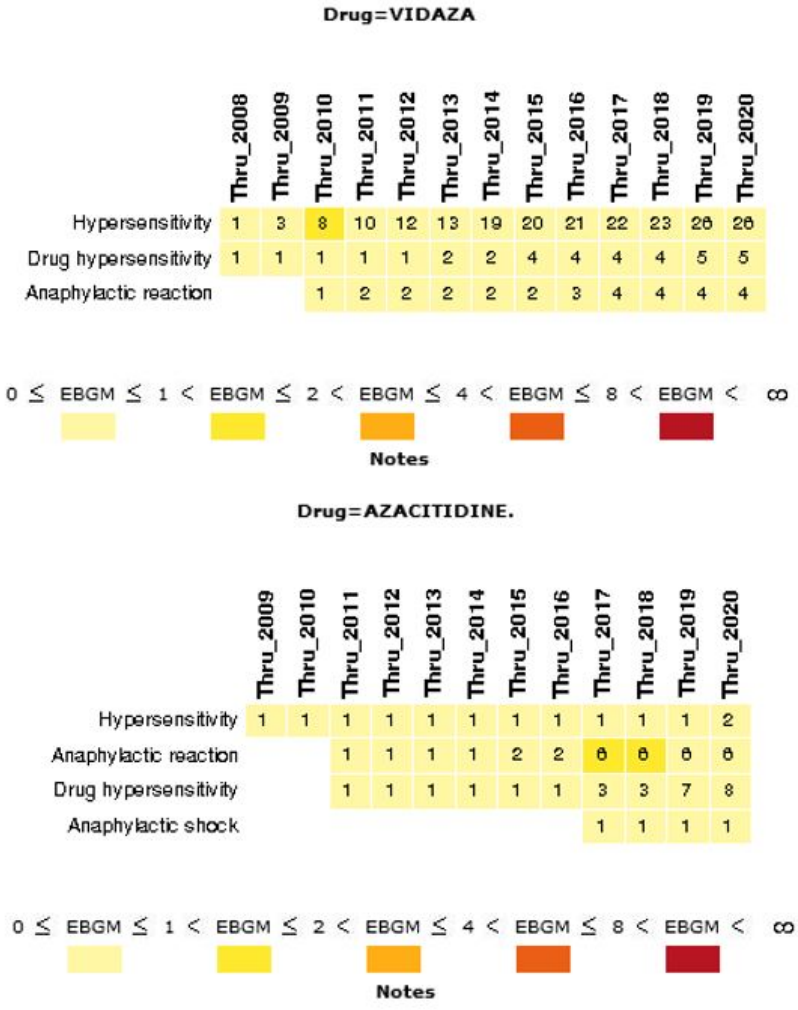
Clinical Reviewer's Comment:

- ***Section 6.2 of the Vidaza USPI describes multiple adverse reactions identified during post-approval use of IV/SC azacitidine. Although these ARs were not observed in the pivotal trial, it is possible that they could occur with postmarket treatment of a large number of patients with continuous dosing of oral azacitidine. Therefore, the ARs should be included in the oral azacitidine USPI.***

- ***The Vidaza USPI includes a contraindication for patients with hypersensitivity to azacitidine and hypersensitivity is described in Section 6.2 under SARs occurring at < 5% in clinical studies of SC or IV Vidaza. A review of the Empirica database (Figure 15)***

shows that hypersensitivity reactions have also been observed in the postmarketing setting. Therefore, a contraindication for hypersensitivity should be included and hypersensitivity should be added to the postmarketing section of the oral azacitidine USPI. Additionally, enhanced pharmacovigilance for hypersensitivity reactions is warranted.

Figure 21. Reports of Hypersensitivity with Vidaza/Azacitidine in the Postmarketing Setting



Source: FDA Analysis

Expectations on Safety in the Postmarket Setting

Safety in the postmarketing setting is expected to be similar to that observed on the clinical trials reviewed in this application. However, it is recognized that once it is approved, its use may not be limited to those with adequate performance status and organ function to be enrolled on the trial. Also, it may be used in populations other than those included in the

indication statement. For these reasons, safety in the postmarket setting is not entirely predictable.

Clinical Reviewer's Comment:

- ***In addition to the potential for hypersensitivity reactions discussed above, the significant safety concern in the postmarketing setting is the lack of interchangeability of oral azacitidine with IV/SC azacitidine. Administration of oral azacitidine and IV/SC azacitidine at labeled doses do not result in equivalent drug exposure. The concern for potential inappropriate off-label substitution of oral azacitidine for IV/SC azacitidine is strengthened by the recent approval of Inquovi, an oral decitabine + cedazuridine product which does have equivalent drug exposure to IV decitabine.***

  - ***Treating patients with a 1:1 exchange of IV/SC azacitidine for oral azacitidine could result in fatal overdose.***

  - ***Treating patients with active MDS (labeled indication for Vidaza) or AML (commonly used off-label to induce remission) with a 1:1 exchange of oral azacitidine for IV/SC would result in ineffective treatment of active disease.***

  - ***Potential for off-label use of oral azacitidine at other dose/schedules:***

    - ***Treatment of MDS – the risk of increased mortality with oral azacitidine at 300 mg QD x 21/28 was discussed 8.3.8 and merits a separate warning.***

    - ***Treatment of AML – there are minimal data to support induction of remission with oral azacitidine at any dose/schedule (see discussion in 8.2.1).***

  Taken together these risks of clinically significant, potentially fatal adverse reactions due to substitution with other azacitidine products merit a warning in the USPI.

- ***Patients with moderate to severe hepatic impairment (HI) were not included in CC-486-AML-001. Given the hepatic metabolism of this drug, patients with severe HI are at higher risk of hepatotoxicity, and the Vidaza USPI includes a warning for use in these patients. The indicated population for oral azacitidine comprises patients who are unable to complete intensive therapy; this population is likely to include patients with severe HI. In the absence of safety and PK data in this population, a PMR for safety and PK data in patients with severe HI and a cautionary statement in the USPI for use this population are warranted.***

8.3.11 Integrated Assessment of Safety

The primary data in support of safety came from CC-486-AML-001 in which 472 patients with

AML in CR or CRi post-induction were randomized to treatment with oral azacitidine 300 mg QD x 14/28 days or placebo. Seventy-four percent of patients in the oral azacitidine arm received at least 6 cycles of therapy while only 58% of patients in the placebo arm remained on study for at least 6 cycles.

On-treatment deaths occurred in 6% of patients treated with oral azacitidine vs 5% in the placebo arm, and one patient on the oral azacitidine arm died due to AML within the first 30 days on study. There was one on-treatment death due to sepsis on the oral azacitidine arm which was considered at least possibly related to study drug.

Overall, 8% of patients on the oral azacitidine arm discontinued treatment due to an adverse event. AEs leading to discontinuation of oral azacitidine were predominantly due to GI toxicity (nausea, diarrhea, vomiting: 6% total) with an additional 1% each due to fatigue and pneumonia.

During Cycles 1-5, adverse events occurring at a greater incidence in the oral azacitidine arm were gastrointestinal toxicities, cytopenias, and fatigue.

- Common (≥ 10%) TEAEs with oral azacitidine occurring at ≥ 2% difference compared to placebo included nausea, vomiting, diarrhea, constipation, fatigue, and abdominal pain.

- For the majority of patients, GI toxicity was manageable by dose interruption and/or use of antiemetics or antidiarrheals during early cycles of therapy. Treatment of ARs with these supportive medications tapered off after the 2nd cycle.

- No Grade ≥ 3 TEAEs occurred in more than 2% of patients in either arm except for vomiting and diarrhea which each occurred in 3% of patients in the oral azacitidine arm.

- As expected, treatment-emergent Grade 3-4 neutropenia and thrombocytopenia were higher in the oral azacitidine arm compared to the placebo arm (40% vs 19% and 16% vs 7%, respectively). In the oral azacitidine arm, these required dose interruption in 27% of patients and dose reduction in 8%.

- Except for hyperuricemia, the incidence of all other treatment-emergent Grade 3-4 laboratory abnormalities was ≤ 1% in patients treated with oral azacitidine.

Common (≥ 10%) adverse reactions with oral azacitidine over the entire course of the study were nausea, vomiting, diarrhea, fatigue/asthenia, constipation, pneumonia, abdominal pain, arthralgia, decreased appetite, febrile neutropenia, dizziness, and pain in extremity.

Data from an additional 36 patients who received oral azacitidine at the same dose and schedule for treatment of active hematologic malignancies were included in a side-by-side comparison. No safety findings were seen in the pivotal trial that were not also reported in the

cohort treated for active hematologic malignancies.

A number of concerns were identified regarding use of oral azacitidine in the post-marketing setting that must be addressed in the USPI.

- Lack of interchangeability – administration of labeled doses of oral azacitidine and IV/SC azacitidine do not result in equivalent drug exposure. The risks of clinically significant, potentially fatal adverse reactions due to substitution with other azacitidine products merit a warning in the USPI.

- Increased mortality in patients with MDS – Vidaza is approved for use in patients with MDS. However, in a randomized placebo-controlled trial, patients with lower-risk MDS treated with oral azacitidine had increased early mortality due predominantly to fatal sepsis. This clinically significant risk merits a warning in the USPI stating that the safety and effectiveness of oral azacitidine for MDS have not been established and use is not recommended outside of controlled trials.

- Postmarketing ARs with Vidaza including hypersensitivity – the safety profile of SC/IV azacitidine has been well established and the Vidaza USPI includes several ARs identified in the postmarketing setting. Although these ARs were not observed in the oral azacitidine trials, with treatment of a wider population with an extended duration of therapy these ARs may be observed in the postmarket setting and should be included in the USPI.

Finally, the indicated patient population comprises patients with AML who are unable to complete intensive curative therapy. This is likely to include patients with moderate to severe hepatic impairment. However, CC-486-AML-001 did not enroll this population. In the absence of data to support safe and appropriate dosing in this population, a PMR for safety and PK data in patients with severe HI and a cautionary statement in the USPI for use this population are warranted.

SUMMARY AND CONCLUSIONS

8.4 STATISTICAL ISSUES

Study CC-486-AML-001 demonstrated a statistically significant improvement in OS with oral AZA compared to placebo. The subgroup analysis results by response status at first achieving response type were generally consistent with overall results; hazard ratio from unstratified Cox regression model was estimated as 0.71 (95% CI: 0.55, 0.9) in the CR population and 0.74 (95% CI: 0.45, 1.2) in the CRi population. However, these subsets were not planned to be formally tested. Consequently, they were not powered for formal comparisons.

The efficacy results were driven primarily by European patients. The subgroup analyses suggested that hazard ratio from unstratified Cox regression model was estimated as 1.09 (95% CI: 0.65, 1.82) in North America and 0.60 (95% CI: 0.46, 0.77) in Europe. The naïve estimate for North American patients should be interpreted with caution due to the small sample size of this subgroup. Subsequent analyses which assumed minimal pooling across the two regions suggested that the hazard ratio for the US is likely to be below 1. Such analyses are exploratory and rely on the assumption of exchangeable treatment effects between the two regions. Additional analyses performed suggested that there was not enough evidence to conclude that there is a significant difference in efficacy between the US and EU.

8.5 CONCLUSIONS AND RECOMMENDATIONS

The review team recommends regular approval of oral azacitidine for the indication "for continued therapy in adult patients with acute myeloid leukemia who achieved first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following intensive induction chemotherapy and are not able to complete intensive curative therapy.

Warnings in the USPI are recommended for the lack of interchangeability between oral azacitidine and SC/IV azacitidine as well as for increased mortality in patients with MDS treated with an unapproved regimen of oral azacitidine. As there are no data on the use of oral azacitidine in patients with moderate to severe hepatic impairment, a PMR is recommended to obtain PK and safety data in this population.

9 ADVISORY COMMITTEE MEETING

This application was not discussed by an advisory committee meeting or external consults.

10 PEDIATRICS

Azacitidine (Vidaza) for intravenous use was granted Orphan Drug Designation for treatment of acute myeloid leukemia in 2008. The active moiety of Onureg is the same as in Vidaza; therefore, this application is exempt from the PREA requirements of a pediatric assessment. There are no data in this submission showing that the oral formulation of azacitidine is superior to the intravenous formulation. Additionally, no data regarding the safety or efficacy of oral azacitidine in children were included in this NDA.

11 LABELING RECOMMENDATIONS

11.1 PRESCRIBING INFORMATION (PI)

The table below summarizes high-level changes to the proposed PI made by FDA.

Highlights of Significant Labeling Changes

Section	Applicant Proposed Labeling	FDA Recommended Labeling
Highlights		
Initial US Approval	Included placeholder (b) (4) for this drug product.	Changed to the Initial U.S. Approval date for a parenteral azacitidine product, (b) (4)
Full Prescribing Information		
Indications and Usage	Included an indication (b) (4)	Modified indication to that of continued treatment in adults with AML who achieved first CR or CRi following intensive induction chemotherapy and at not able to complete intensive consolidation therapy, based on the study population and the study design
Dosage and Administration, Important Administration Information	…	Added 'Important Administration Information' subsection to state 'Do not substitute TRADENAME for intravenous or subcutaneous azacitidine' based on risk of loss of effectiveness or fatal adverse reactions with substitution.
Dosage and Administration, Recommended Dosage	(b) (4)	Removed (b) (6)' from recommended dosage, (b) (6) Revised (b) (4) to disease progression or unacceptable toxicity, (b) (4)
Dosage and Administration, (b) (4)	(b) (4)	Omitted this subsection and included administration information with the recommended dosage, because FDA preference is to include the administration with the recommended dosage when only one recommended dosage subsection is included in the labeling. Created a separate subsection to discuss substitution as described above. Add instruction for prophylactic antiemetics and to withhold TRADENAME if ANC value is low on day 1 of any cycle.

Highlights of Significant Labeling Changes

Section	Applicant Proposed Labeling	FDA Recommended Labeling
Dosage and Administration, (b) (4)	(b) (4)	Removed (b) (4)
Dose and Administration, (b) (4)	…	Added monitoring of CBC and revised the table for consistency with the dose modifications in the phase 2 protocol. Changed (b) (4) to a 3-column format for consistency with recently approved labeling.
Warnings and Precautions	…	Added subsection 5.1, Risks of Substitution of Other Azacitidine Products to describe the risk of loss of effectiveness or fatal adverse reactions with substitution of oral and parenteral azacitidine products.
Warnings and Precautions, Myelosuppression	(b) (4)	Included the percentage of patients with neutropenia and thrombocytopenia based on the lab dataset, (b) (4) and the percentage of patients who required a dose reduction or permanent discontinuation of TRADENAME for myelosuppression.
Warnings and Precautions, (b) (4)	…	Removed (b) (4)
Warnings and Precautions, Embryo-Fetal Toxicity	Recommended that females of reproductive potential use effective contraception for at least (b) (4) months after the last dose.	Revised to at least 6 months after the last dose based on recommendations found in: Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations [May 2019].
Adverse Reactions, Clinical Trials Experience	…	Revised the information provided in this subsection to reflect the 3-month safety update report. Added the percentage of patients exposed for 6 months and 1 year based on the recommendations found in: Adverse Reactions Section of Labeling guidance [January 2006]. Added a description of fatal adverse reactions. Modified the most common list to describe the entire treatment course.

Highlights of Significant Labeling Changes

Section	Applicant Proposed Labeling	FDA Recommended Labeling
		Revised the tabular summaries of the adverse reactions and laboratory abnormalities to the first 5 cycles. Added percentage of patients who experienced myelosuppression throughout the entire treatment period. Modified format and content based on OOD current labeling recommendations.
Adverse Reactions, Postmarketing Experience	…	Added to summarize the adverse reactions that have been identified during postapproval use of intravenous or subcutaneous azacitidine that could occur with this product.
Use in Specific Populations, Pregnancy	Summarized results of early embryotoxicity studies conducted in mice and rats following intraperitoneal administration of azacitidine with exposure multiple (b) (4)	Revised exposure multiples to 'at doses less than recommended human daily dose' because of the substantial differences in exposure between oral and parenteral azacitidine.
Use in Specific Populations, Lactation	Recommended advising women not to breastfeed for (b) (4) after the last dose.	Modified to 1 week based on the elimination half-live.
Use in Specific Populations, Geriatric Use	(b) (4)	Revised to provide the percent of patients who received oral azacitidine that were 65 years and older and 75 years and older and for consistency with 21 CFR 201.57 (c)(9)(v)(B)(2)].
Nonclinical Toxicology, Carcinogenesis, Mutagenesis, Impairment of Fertility	Summarized results of carcinogenicity studies and reproductive effects of azacitidine in mice and rats following intraperitoneal administration with exposure multiple (b) (4)	Revised exposure multiples to 'at doses less than recommended human daily dose' because of the substantial differences in exposure between oral and parenteral azacitidine.
(b) (4)	…	Removed, because this section is not needed (b) (4)
Clinical Studies	…	Added randomization stratification factors. Removed (b) (4) Added induction response and disease status at baseline. Removed (b) (4)

Highlights of Significant Labeling Changes

Section	Applicant Proposed Labeling	FDA Recommended Labeling
		(b) (4) Removed (b) (4) . Removed (b) (4) Removed (b) (4)

11.2 PATIENT LABELING

Updated in accordance with the changes in the USPI listed above.

12 RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

No safety issues were identified that would warrant consideration of a REMS.

13 POSTMARKETING REQUIREMENTS AND COMMITMENTS

Postmarketing Requirements

PMR-1 Submit the final report and datasets from a clinical pharmacokinetic study to determine a safe and appropriate dose of oral azacitidine in patients with moderate and severe hepatic impairment that may inform product labeling. Design and conduct the study in accordance with the FDA Guidance for Industry titled *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.*

14 DIVISION DIRECTOR (DHM1)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

Angelo de Claro, MD

Director, Division of Hematologic Malignancies (DHM1)

15 APPENDICES

15.1 REFERENCES

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15.2 FINANCIAL DISCLOSURE

Financial disclosures were submitted for 4 investigators who received between $10-50k per person from Celgene. The clinical sites to which the investigators belonged enrolled (b) (6) (b) (6) patients out of a total of 472 patients enrolled on CC-486-AML-001 making the contribution to the study population (b) (6)% at each site. Enrollment at these sites would have minimal impact on the overall findings of the study.

Covered Clinical Study (Name and/or Number): CC-486-AML-001

Was a list of clinical investigators provided:	Yes x ☐	No(Request list from Applicant)
Total number of investigators identified: 1733		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 4		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 4 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Applicant of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes x	No (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes x	No (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1729		
Is an attachment provided with the reason:	Yes x	No (Request explanation from Applicant)

15.3 NONCLINICAL PHARMACOLOGY/TOXICOLOGY

None

15.4 OCP APPENDICES

15.4.1 Pharmacometrics Review

Applicant's PPK/ER Analysis of Azacitidine in Patients with Acute Myeloid Leukemia Who Have Achieved Complete Remission

Objectives

PPK analysis: To develop a PopPK model to characterize oral azacitidine concentration-time profiles, to predict Bayesian individual PK parameters for exposure-response (E-R) analysis.
E-R analysis: To evaluate exposure-efficacy relationship for OS and PFS, and to evaluate exposure-safety relationship for Grade ≥ 3 AEs.

Data: Azacitidine PK data were collected from 300 mg CC-486 (oral azacitidine) concentration data from two Phase 1 studies with intensive data (AZA-MDS-004 and CC-486-CAGEN-001) and one Phase 3 study with sparse data (CC-486-AML-001). A total of 286 subjects and 1933 concentration observations were included in the PopPK modeling. E-R analyses were based on 234 subjects on placebo and 225 subjects on azacytidine from CC-486-AML-001.

PPK Results:

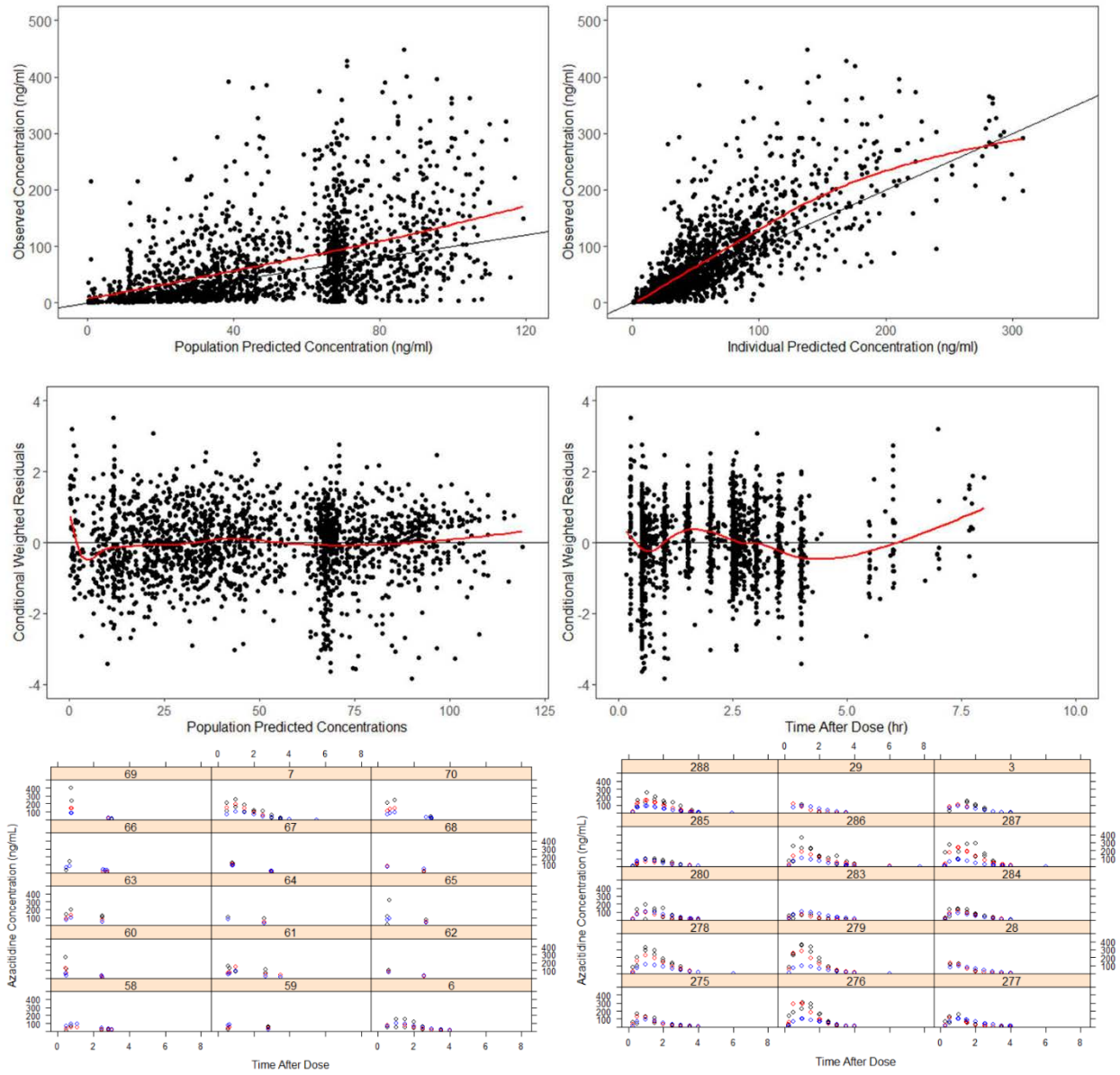
Azacitidine PK were adequately described by a one-compartment structure model with first-order absorption incorporating a lag time and first-order elimination with GOF shown in **Figure 22**. The PPK estimates are listed in **Table 59**.

Table 59: Parameter Estimates of the Final Population Pharmacokinetics Model of Azacitidine

Parameter (Unit)	Estimate	RSE%
CL/F (L/hr)	1530	4.36
V/F (L)	889	8.79
KA (hr^{-1})	1.04	5.76
LAG (hr)	0.215	1.88
CLcr on CL/F	0.321	34.89
Inter-Individual variability		
IIV in CL/F (%)	54.5	10.95
IIV in V/F (%)	84.8	14.05
IIV in KA (%)	38.1	18.90
Residual variability		
RV for MDS-004 (%)	49.0	18.54
RV for CAGEN-001(%)	57.4	15.08
RV for AML-001 (%)	90.5	7.86

CL/F = apparent clearance from the central compartment; IIV = interindividual variability; ka = first-order rate of absorption; RSE = % relative standard error; RV = residue variability; V/F = apparent volume of distribution.
Source: Table 8 of Applicant's PPK-ER report.

Figure 22: Goodness of Fit of the Population Pharmacokinetics Model of Azacitidine



In the top and middle panels, the solid line represents the identity line or zero line. The red dashed line represents the locally weighted scatterplot smoothing line. The bottom two panels are representative plots of individual fittings of sparse and dense data where black dots are observations and red dots are predictions.
Source: Figure 6 of Applicant's PPK-ER report for the top and middle panels and Section 1.3.7 of Appendix A for the bottom 2 panels.

CLcr was statistically significant covariate on CL/F, however, its contribution to the IIV of CL/F was marginal, reducing the IIV from 55.9 to 54.5% in the final model, which was not deemed to be clinically relevant. None of other tested covariates (including age, body mass index, weight, sex, race, ALT, and AST) had statistically significant effect on oral azacitidine PK.

FDA Reviewer's Comments: *in general, the Applicant's final PPK model appears fit-for-purpose, but limited by the following:*

- *Minor model-misspecification is noted based on the diagnostic plots, with data unevenly distributed above the identity line, indicating the potential underestimation of azacitidine exposure, especially C_{max} as shown in the two bottom panels of* ***Figure 22****. Therefore, the exposure-response analysis results using C_{max} should be interpreted with caution.*
- *The Applicant model did not include covariance η_{12} between η_1 and η_2 to account for high correlation between CL/F and V/F. After the addition of η_{12}, the objective function value (OFV) decreased by 36.9 as shown in* ***Table 60****, with inter-individual variability (IIV) increased by 1.1% in CL/F and decreased by 4.4% in V/F, respectively.*

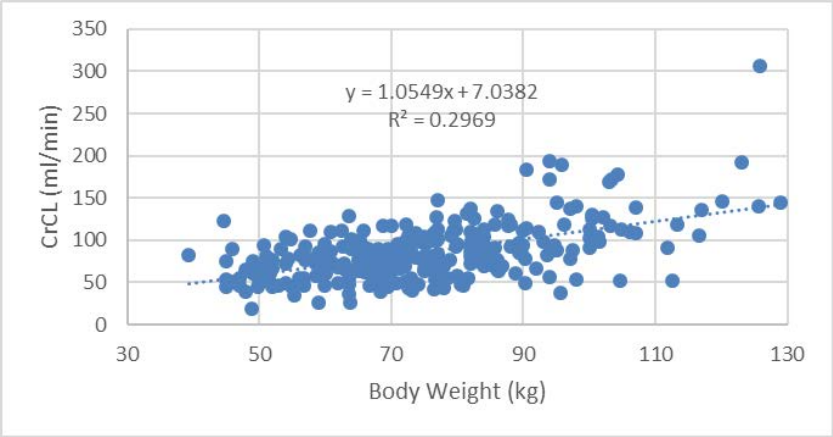
Table 60: OFV and Parameter Estimates Comparison across Different Covariate Models

	OFV	CL/F (L/hr)	V/F (L)	IIV in CL/F (%)	IIV in V/F (%)	CL/F shrinkage (%)	V/F shrinkage (%)
Applicant's base model	1427.2	1510	891	55.9	84.8	22	32
Revised base model (η_{12} added)	1390.3	1570	1010	57.0	80.4	19	27
CrCL on CL with revised base model	1385.8	1580	997	55.5	80.5	20	28
BW on CL with revised base model (reviewer's final model)	1381.7	1560	1390	55.9	66.4	19	27

Source: FDA reviewer's analysis.

- *As creatinine clearance (CrCL) correlates with body weight and imbalance of body weight was noted across the renal function category (median weights were 82, 70, 67 and 59 kg in normal to severe renal impairment categories per CrCL classification, respectively), it is likely that the apparent effect of CrCL on PK also reflected the difference in weight.* ***Figure 23*** *shows the correlation between body weight and CrCL on a continuous scale. As such, the reviewer conducted sensitivity analysis by replacing CrCL effect on CL/F with body weight. Body weight was identified as a significant covariate of CL/F , with OFV decrease further by 4.1 compared to the CrCL model. The parameter estimates for reviewer's final model are listed in* ***Table 61****.*

Figure 23: Correlation between Body Weight and Creatinine Clearance



Source: FDA reviewer's analysis based on applicant's PPK dataset.

Table 61: Parameter Estimates of Reviewer's Final Model with Covariance Included

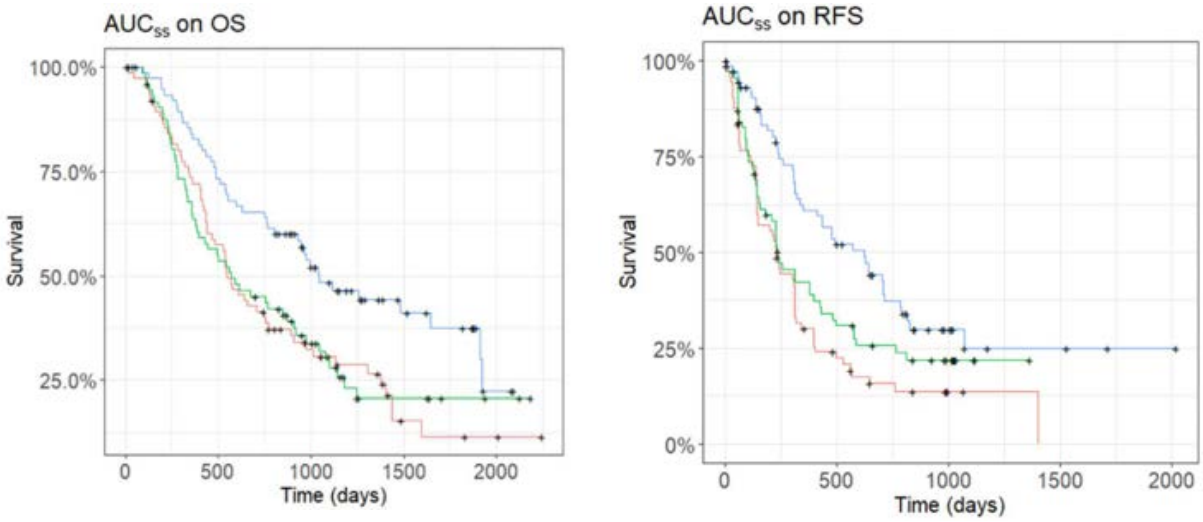
Parameter (Unit)	Estimate	RSE%
CL/F (L/hr)	1570	4.15
V/F (L)	1390	8.64
KA (hr^{-1})	1.57	6.71
LAG (hr)	0.215	2.01
BW on CL/F	0.414	44.1
Inter-Individual variability		
IIV in CL/F (%)	55.9	5.47
IIV in V/F (%)	66.4	6.81
IIV in KA (%)	67.4	10.8
Residual variability		
RV for MDS-004 (%)	48.7	9.20
RV for CAGEN-001(%)	57.2	7.45
RV for AML-001 (%)	92.1	3.89

CL/F = apparent clearance from the central compartment; IIV = interindividual variability; ka = first-order rate of absorption; RSE = % relative standard error; RV = residue variability; V/F = apparent volume of distribution.
Source: FDA reviewer's analysis.

EXPOSURE-EFFICACY RESULTS:

The E-R relationship for OS and RFS was initially explored by Kaplan-Meier curves stratified by azacitidine exposure (AUC_{SS}, $C_{ave,C1-C6}$, and $C_{max,SS}$) tertile groups and followed by Cox regression analyses of exposure parameters as a continuous covariate. The regression analyses identified azacitidine AUC_{SS} as a statistically significant predictor for OS and azacitidine AUCss and $C_{max,SS}$ as statistically significant predictors for RFS, suggesting that increased intensity of exposure is beneficial for OS and RFS (**Figure 24**).

Figure 24: Kaplan-Meier Curve for Overall survival and Relapse-Free Survival by Azacitidine Exposure

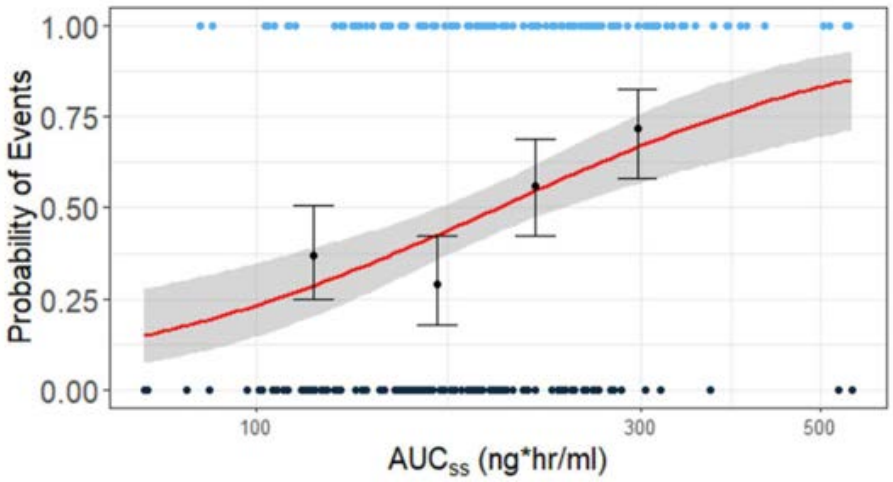


Source: Figures 9 and 10 of Applicant's PPK-ER report.

EXPOSURE-SAFETY RESULTS:

Relationship of the CC-486 PK exposure parameters (AUC_{C1-C6}, AUCss, $C_{ave,C1-C6}$ and $C_{max,ss}$) and occurrence of Grade ≥ 3 AEs of interest were initially explored by visual inspection and ANOVA and followed by logistic regression analyses. Regression analysis identified logAUCss, $logAUC_{C1-C6}$ and $logC_{max,ss}$ as statistically significant factors affecting the probability of neutropenia of Grade ≥ 3 (**Figure 25**); and $logC_{ave,C1-C6}$ as a statistically significant factor affecting the probability of nausea of Grade ≥ 3.

Figure 25: Logistic Model of Probability of Neutropenia of Grade ≥ 3



Source: Figure 12 of Applicant's PPK-ER report.

FDA Reviewer's Comments: *The Applicant's E-R analyses using AUCss are acceptable. Due to potential confounding effect of dose adjustment on efficacy/safety outcome, AUC of the first dose (equivalent to AUCss calculated by Applicant's method) could be the most relevant exposure metrics for E-R analysis.*

Reviewer's Independent Analysis

Objectives: Based on reviewer's sensitivity analysis on the final population PK model, body weight was identified as important covariate on clearance of azacitidine, with higher exposure associated with lower body weight. Given that the proposed dosing regimen is a fixed dose, the reviewer conducted exploratory analyses to assess the potential impact of body weight on azacitidine efficacy or safety.

Data: PK, efficacy and safety data from study CC-486-AML-001. The following key efficacy and safety endpoints were evaluated: overall survival, relapse free survival, Grade 3/4 neutropenia, and dose reduction due to AE.

Method: R v3.5.0 was used to merge data, perform analyses and visualize the results.

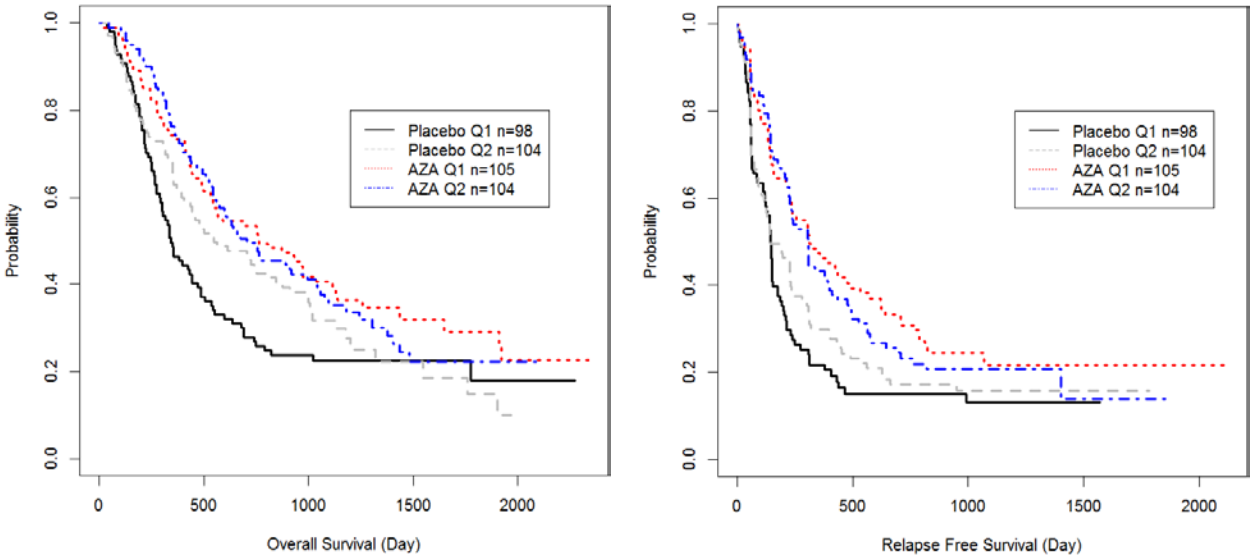
Results:

Kaplan-Meier Plots of relapse free survival (RFS) and overall survival (OS) by treatment arm and body weight groups (split by median body weight of 72.9 kg) are shown in **Figure 26**. In patients with higher body weight (Q2: ≥72.9 kg), the separation in OS and RFS between azacitidine and placebo appeared to be smaller than the that in patients with lower body weight (Q1: < 72.9 kg), indicating worse efficacy in patients with higher body weight.

On the other hand, patients with low baseline body weight (Q1) appeared to have higher incidence of treatment emergent Grade 3 or 4 neutropenia (Table 62), and higher probability to reduce azacitidine dose (Figure 27).

However, since there are other baseline factors that may have contributed to the difference in efficacy and safety between body weight groups, the effect is not considered clinically significant to warrant dose adjustment. The need for dose optimization for azacitidine based on body weight should be further evaluated as additional data from ongoing or planned studies becomes available.

Figure 26: Kaplan-Meier Plots of Overall Survival (Left Panel) and Relapse Free Survival (Right Panel) by Treatment and Body Weight Subgroups

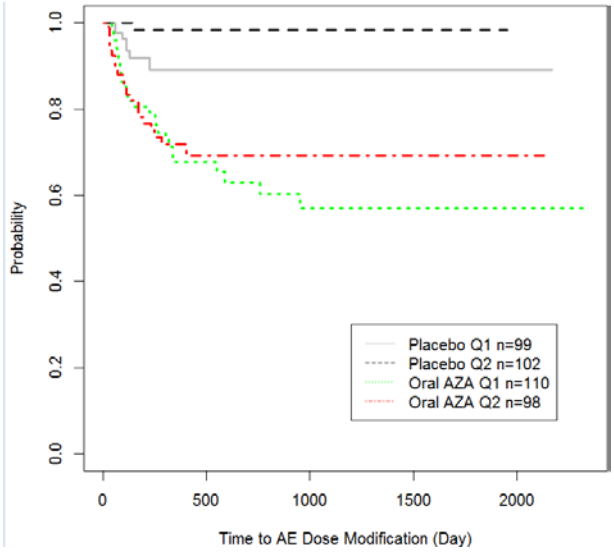


Source: FDA reviewer's analysis based on adtte.xpt and adsl3.rda for CC-486-AMLM-001

Table 62: Treatment Emergent ≥ Grade 3 Neutropenia Rate by Body Weight Median for Study CC-486-AML-001

Body Weight Subgroups	BW < 72.9 kg	BW ≥ 72.9 kg
Placebo	22.3% (25/112)	20.7% (25/121)
Oral AZA	47.5% (58/122)	32.2% (37/115)
Source: FDA reviewer's analysis based on adae.xpt and adsl3.rda for CC-486-AMLM-001		

Figure 27: Time to Adverse Event Related Dose Modification by Treatment and Body Weight Subgroups



Source: FDA reviewer's analysis based on adex.xpt for CC-486-AMLM-001 and poppknnonmem.xpt.

Appendix: FDA Reviewer's Analysis for Risk Factor Distribution Across Exposure Tertiles

Using Applicant's exposure-response dataset for efficacy, subject baseline and demographic factors were summarized by AUCss quartile to investigate whether those were equally distributed across the exposure range. The distributions of these factors are provided in Table 63. In general, covariates were evenly distributed across the AUCss quartiles Q1- Q3, except for imbalance in baseline body weight, which is expected from the body weight effect on PK identified by the reviewer's sensitivity analysis .

Table 63: Distribution of Baseline Factors Across AUC Tertiles vs Placebo

Baseline Factors (%)	Placebo	AUCss Q1	AUCss Q2	AUCss Q3
Age ≥ 65Yr	70	65	71	77
Age 55-64Yr	30	35	29	23
Body weight < median	48	38	53	65
Body weight ≥ median	52	62	47	35
Europe Region	63	64	66	81
Non_Europe Region	37	36	34	19
Hispanic Latin	14	19	17	17
Not Hispanic Latin	86	81	83	83
White	84	91	92	91
Non-White	16	9	8	9
Baseline Response is CR	77	84	71	79
Baseline Response is CRi or other	23	16	29	21
Prior consolidation therapy used	82	80	76	76
No prior consolidation therapy used	18	20	24	24
Primary AML	92	93	86	88
Secondary AML	8	7	14	12
Prior MDS	7	7	11	12
No prior MDS	93	93	89	88
Cytogenetic Risk Intermediate	87	91	83	84
Cytogenetic Risk Poor	13	9	17	16
ECOG≤1	93	91	91	92
ECOG≥2	7	9	9	8
Bone marrow % of blasts < median	43	42	50	48

Baseline Factors (%)	Placebo	AUCss Q1	AUCss Q2	AUCss Q3
Bone marrow % of blasts ≥ median	57	58	50	52
Absolute Neutrophil Count < median	52	46	43	53
Absolute Neutrophil Count ≥ median	48	54	57	47
Hemoglobin < Median	53	50	37	43
Hemoglobin ≥Median	47	50	63	57
White blood cell count < median	59	51	53	53
White blood cell count ≥ median	41	49	47	47
Platelet < median	44	51	58	55
Platelet ≥ median	56	49	42	45
Time Since Induction to CR/CRi < Median	49	39	50	41
Time Since Induction to CR/CRi ≥ Median	51	61	50	59
Time Since Induction to Rand < median	49	46	55	52
Time Since Induction to Rand ≥ median	51	54	45	48
Time since 1st CR/CRi at randomization < median	46	49	57	49
Time since 1st CR/CRi at randomization ≥ median	54	51	43	51
Time since AML diagnosis at randomization <median	48	41	53	51
Time since AML diagnosis at randomization ≥median	52	59	47	49

Note: AUCss Q1 is between 73.0 and 161.3 ng*h/mL, AUCss Q2 is between 162.2 and 236.2 ng*h/mL, and AUCss Q3 is between 238.1 and 546.4 ng*h/mL.
Source: FDA reviewer's analysis based on adsl3.rda and emod2.xpt.

15.4.2 Bioanalytical

The quantitative analysis of CC-486 in plasma and urine was accomplished by validated high-performance liquid chromatography (HPLC) with tandem mass spectrometric detection (LC-MS/MS) methods.

Table 64. Summary of bioanalytical methods used in CC-486 clinical program

Matrix	Analyte	Method validation study report	Bioanalytical Laboratory	Calibration Range (ng/mL)	LLOQ (ng/mL)	Accuracy (%RE)	Precision (%CV)
Plasma fortified with tetrahydrouridine (THU)	azacitidine	(b) (4) Study 7781-101 (full validation)	(b) (4)	1.00-1000	1.00	-0.1 to 8.5 (inter-run); -2.8 to 8.9 (intra- run)	≤ 6.9% (intra-run); ≤ 6.1% (inter-run)
		(b) (4) Study 8203 550 (AZACITIDINE - DMPK-003, partial validation)	(b) (4)	1.00-1000	1.00	1.3% to 5.2% (inter-run); -3.0% to 9.0% (intra- run)	≤ 7.2 % (intra-run); ≤ 8.0 % (inter- run)

Matrix	Analyte	Method validation study report	Bioanalytical Laboratory	Calibration Range (ng/mL)	LLOQ (ng/mL)	Accuracy (%RE)	Precision (%CV)
Urine fortified with tetrahydrouridine (THU)	azacitidine	(b) (4) Study 8203-729 (Azacitidine-DMPK-004, partial validation)	(b) (4)	1.00- 2000	1.00	-2.0 to 4.0 (inter-run); -3.0 to 6.0 (intra- run)	≤ 8.8 % (intra-run); ≤ 6.9 % (inter- run)

Source: Summary of Biopharmaceutical Studies and Associated Analytical Methods (M2.7.1)

The performance of the bioanalytical methods in individual clinical studies is summarized in **Table 65.**

Table 65: Summary of Bioanalytical Method Performance for Analysis of Clinical Study Samples

Study	Bioanalytical Laboratory	Bioanalytical Method	Bioanalysis Report	Analyte	Biological Matrix	LLOQ (ng/mL)	Accuracy (%RE)	Precision (%CV)
AZA PH US 2007 CL005	(b) (4)	7781-103-Legacy (7781-103)	AZA PH US 2007 CL005-BA	CC-486	Urine	1.00	0.0 to 1.8	≤ 8.8
		7781-101-Legacy (7781-101)	AZA PH US 2007 CL005-BA-2	CC-486	Plasma–K_2EDTA	1.00	-1.7 to 3.0	≤ 8.9
CC-486-CAGEN-001	(b) (4)	AZACITIDINE - DMPK-003 (82 03550)	CC-486-CAGEN-001-BA	CC-486	Plasma–K_2EDTA with THU	1.00	0.0 to 1.8	≤ 6.9
AZA-MDS-004	(b) (4)	AZACITIDINE - DMPK-003 (82 03550)	AZA-MDS-004-BA	CC-486	Plasma–K_2EDTA with THU	1.00	-0.7 to 6.0	≤ 8.4%
CC-486-AML-001	(b) (4)	AZACITIDINE - DMPK-003 (82 03550)	CC-486-AML-001-BA	CC-486	Plasma–K_2EDTA with THU	1.00	TBD, study ongoing	TBD, study ongoing

Source: Module 2.7.1 Summary of Biopharmaceutical Studies and Associated Analytical Methods, Table 18 and respective study bioanalysis reports.

15.5 ADDITIONAL STATISTICAL ANALYSES

15.5.1 Subgroup Analysis of OS

Forest Plot of OS by Demographics and Disease-related Characteristics

Figure 28. Forest Plot of OS by Demographics (ITT)

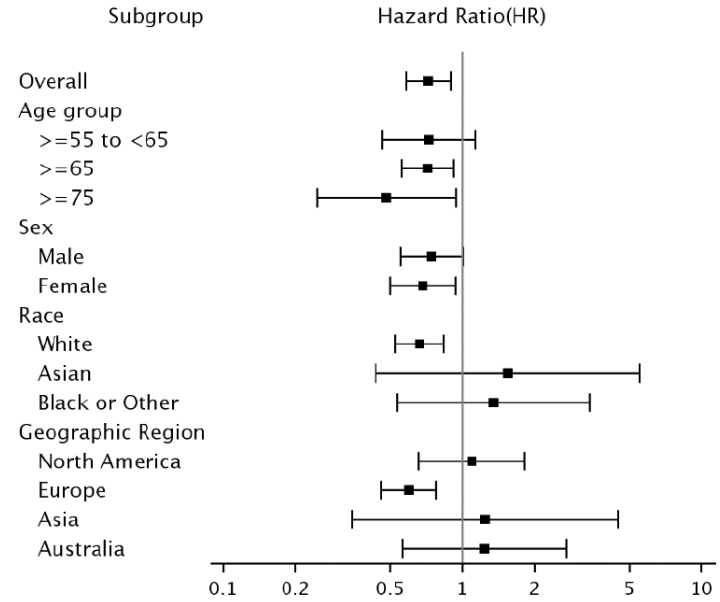
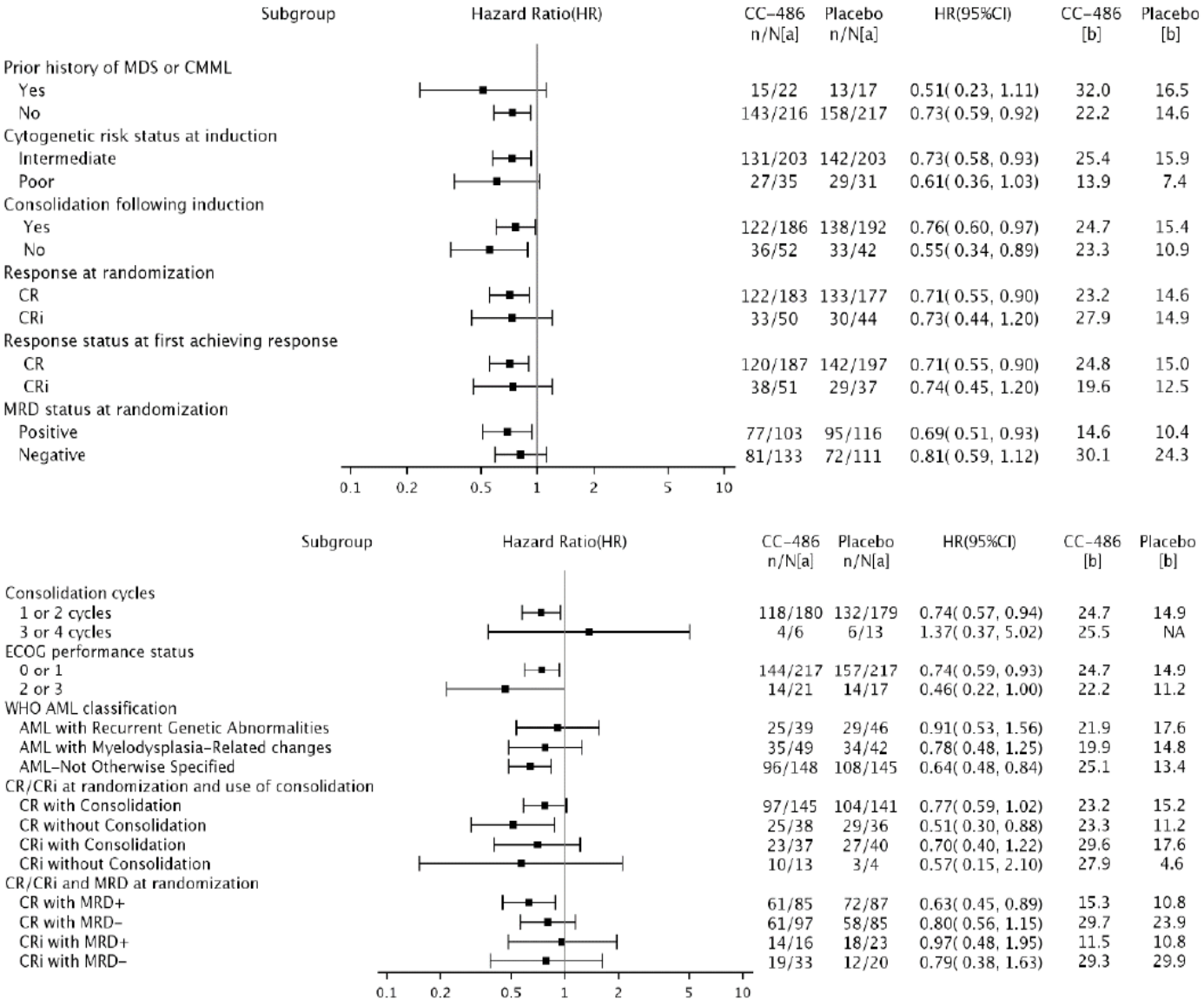


Figure 29. Forest Plot of OS by Disease Characteristics (ITT)

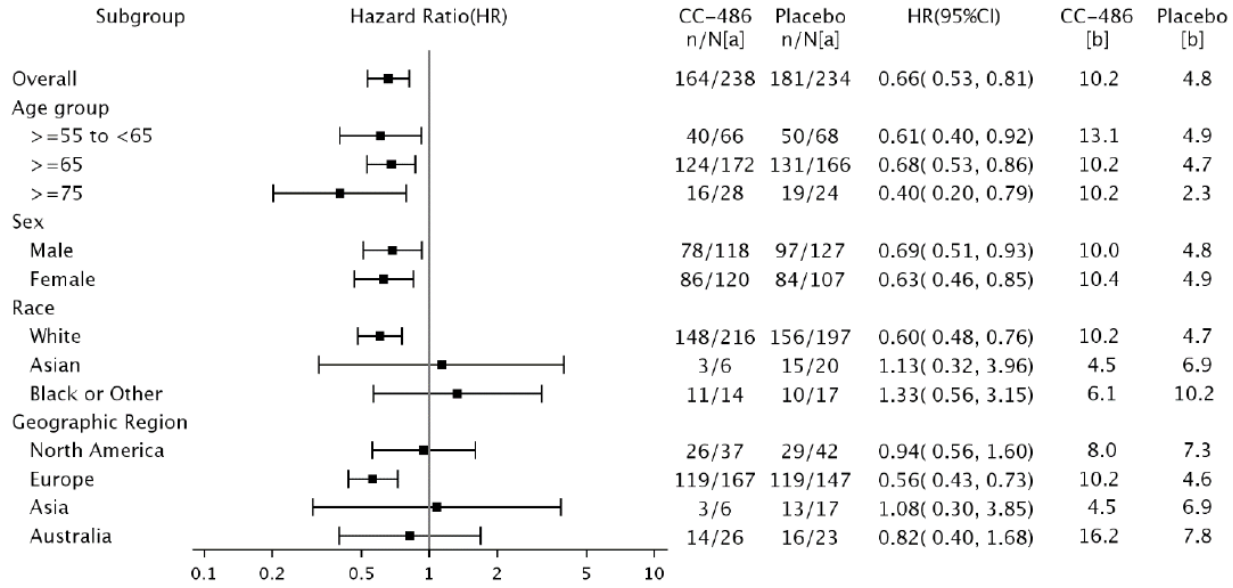


Source: Figure 6 in the Applicant's Statistical Analysis Plan on Page 100.

15.5.2 Subgroup Analysis of RFS per Applicant Definition

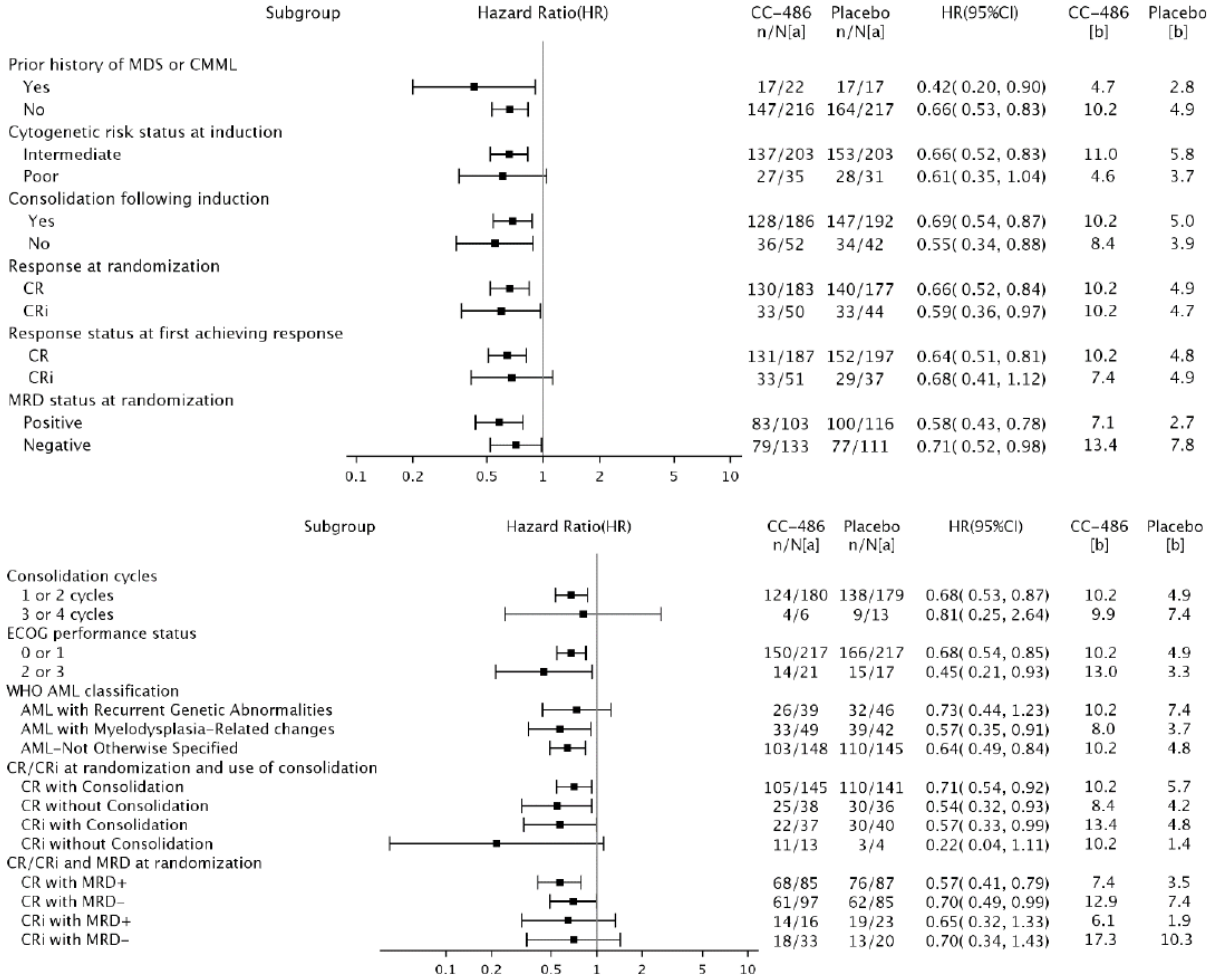
Forest Plot of RFS by Demographics and Disease-related Characteristics

Figure 30. Forest Plot of RFS by Demographics (ITT)



Source: Figure 8 in the Applicant's Statistical Analysis Plan on Page 107.

Figure 31. Forest Plot of RFS by Disease Characteristics (ITT)



Source: Figure 9 in the Applicant's Statistical Analysis Plan on Page 108.

Subgroup Analysis of RFS by Region

Table 66. Subgroup Analysis of RFS by Region

Region	Europe		North America		Other	
Parameter	Placebo N=147	Oral AZA N=167	Placebo N=42	Oral AZA N=37	Placebo N=45	Oral AZA N=34
Subjects with event, n (%)	119 (81%)	119 (71%)	29 (69%)	26 (70%)	33 (73%)	19 (56%)
Subjects censored, n (%)	28 (19%)	48 (29%)	13 (31%)	11 (30%)	12 (27%)	15 (44%)
Hazard Ratio (95% CI) [1]	0.52 (0.4, 0.68)		1.09 (0.6, 2)		0.57 (0.3, 1.07)	
Hazard Ratio (95% CI) [2]	0.56 (0.43, 0.73)		0.94 (0.56, 1.6)		0.78 (0.44, 1.37)	

[1] Estimated with Cox proportional hazard model and log-rank test stratified by age at time of induction therapy (55 to 64 vs. ≥65 years), cytogenetic risk category at time of induction therapy (intermediate risk vs. poor risk) and received consolidation therapy following induction therapy (yes vs. no).
[2] Estimated with unstratified Cox proportional hazard model and log-rank test.

Source: Reviewer's analysis.

Subgroup Analysis of RFS by Number of Consolidation Cycles

Table 67. Subgroup Analysis of RFS by Number of Consolidation Cycles

Number of Consolidation Cycles	No		1 Cycle		2 Cycles		3 Cycles	
Parameter	**Placebo N=42**	**Oral AZA N=52**	**Placebo N=102**	**Oral AZA N=110**	**Placebo N=77**	**Oral AZA N=70**	**Placebo N=77**	**Oral AZA N=70**
Subjects with event, n (%)	34 (81%)	36 (69%)	79 (77%)	84 (76%)	59 (77%)	40 (57%)	59 (77%)	40 (57%)
Subjects censored, n (%)	8 (19%)	16 (31%)	23 (23%)	26 (24%)	18 (23%)	30 (43%)	18 (23%)	30 (43%)
Hazard Ratio (95% CI) [1]	0.55 (0.34, 0.89)		0.71 (0.52, 0.97)		0.57 (0.38, 0.87)		0.84 (0.21, 3.33)	
Hazard Ratio (95% CI) [2]	0.55 (0.34, 0.88)		0.72 (0.53, 0.99)		0.58 (0.38, 0.86)		0.81 (0.25, 2.64)	

[1] Estimated with Cox proportional hazard model and log-rank test stratified by age at time of induction therapy (55 to 64 vs. ≥65 years), cytogenetic risk category at time of induction therapy (intermediate risk vs. poor risk) and received consolidation therapy following induction therapy (yes vs. no).
[2] Estimated with unstratified Cox proportional hazard model and log-rank test.

Source: Reviewer's analysis.

15.6 FDA GROUPED TERMS

- Abdominal pain – Abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, gastrointestinal pain
- Fatigue – Asthenia, fatigue
- Pneumonia – Broad SMQ Infective Pneumonia

NDA Multidisciplinary Review and Evaluation
NDA 214120
Onureg (azacitidine tablets)

Signatures

DISCIPLINE	REVIEWER	OFFICE/ DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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Clinical Pharmacology Team Leader	Ruby Leong, PharmD	OCP/DCPI	Sections: 6	**Select one:** ___ Authored X Approved
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Clinical Pharmacology Division Director	Brian Booth, PhD	OCP/DCPI	Sections: 6, 15.4	**Select one:** ___ Authored X Approved
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Clinical Team Leader	Donna Przepiorka, MD, PhD	OOD/DHMI	Sections: 2, 3, 7, 8.1, 8.2, 8.3, 8.5, 9, 10, 11, 12, 15.1, 15.2, 15.6	**Select one:** ___ Authored X Approved
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Statistical Reviewer	Xin Wang, PhD Xin Wang -S Digitally signed by Xin Wang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Xin Wang -S, 0.9.2342.19200300.100.1.1=2002936169 Date: 2020.08.21 09:19:48 -04'00'	OB/DBIX	Sections: 7, 8.1, 8.2, 8.4, 8.5, 15.5	**Select one:** X Authored ___ Approved
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Statistical Team Leader	Jonathon Vallejo, PhD	OB/DBIX	Sections: 7, 8.1, 8.2, 8.4, 8.5, 15.5	**Select one:** ___ Authored X Approved
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Division Director (OB)	Thomas Gwise, PhD	OB/DBIX	Sections: 7, 8.1, 8.2, 8.4, 8.5, 15.5	**Select one:** ___ Authored X Approved
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Associate Director for Labeling	Stacy Shord, PharmD	OOD	Sections: 11	**Select one:** X Authored ___ Approved
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NDA Multidisciplinary Review and Evaluation
NDA 214120
Onureg (azacitidine tablets)

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Pharmacometrics Team Leader	Lian Ma, PhD	OCP/DPM	Sections: 15,4	**Select one:** ___ Authored X Approved
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Division Director (Clinical)	Angelo de Claro, MD	OOD/DHMI	Sections: All	**Select one:** ___Authored X Approved
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