Official Title of Study:

A Phase 2, Open-Label, Single-Arm Rollover Study to Evaluate Long-Term Safety in Subjects Who Participated in other Celgene Sponsored CC-486 (Oral Azacitidine) Clinical Trials in Hematological Disorders

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A PHASE 2, OPEN-LABEL, SINGLE-ARM ROLLOVER STUDY TO EVALUATE LONG-TERM SAFETY IN SUBJECTS WHO PARTICIPATED IN OTHER CELGENE SPONSORED CC-486 (ORAL AZACITIDINE) CLINICAL TRIALS IN HEMATOLOGICAL DISORDERS

PROTOCOL NUMBER:	**CC-486-GEN-001**
COMPOUND NUMBER:	**CC-486 (also known as BMS-986345)**
DATE FINAL:	**31-MAR-2015**
AMENDMENT 1.0 DATE FINAL	**27 FEB 2023**
EudraCT NUMBER:	**2023-503272-25-00**
IND NUMBER:	**074618**
SPONSOR NAME/ ADDRESS:	Celgene Corporation 86 Morris Avenue Summit, NJ 07901

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CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

[redacted]

Signature [redacted] **dd mmm yyyy**

[redacted]

Printed Name of Celgene Therapeutic Area Head and Title

By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Site Principal Investigator	**dd mmm yyyy**
Printed Name of Site Principal Investigator **Institution Name:**_____ By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Celgene representatives, the Declaration of Helsinki, International Conference on Harmonisation (ICH) Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 1.0:

As of 01 Jan 2023, one subject in the United States (US) continues to receive CC-486, and there are no subjects in the survival follow-up phase of this study. This protocol was amended to allow rollover into this study for subjects outside of the US who are receiving single agent CC-486 in other Celgene clinical trials, tolerate the protocol-prescribed regimen, and in the opinion of the Investigator, may derive clinical benefit from continuing treatment with CC-486.

Additional changes include updates of disease and compound background, investigational product dose modification, information about permitted and prohibited concomitant medications according to the current version of the Investigator's Brochure (IB), and CC-486 product information.

Methods of contraception have been updated in the inclusion criteria for females of childbearing potential (FCBP) and male subjects who are sexually active with FCBP according to the latest recommendation for pregnancy prevention for subjects treated with CC-486, which was found to be both teratogenic and fetotoxic in pre-clinical studies.

Currently, there are no Celgene-sponsored CC-486 clinical trials in solid tumors that may potentially transition subjects into this rollover study; therefore, the language related to solid tumor studies and disorders has been removed from the protocol.

The Protocol Summary was updated to reflect the changes made throughout the protocol.

The revision of this protocol amendment applies to all subjects currently enrolled.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 1.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Throughout the protocol	Table and section numbers updated.	Administrative update.
Title Page	Title updated to remove solid tumors and add the compound number and EudraCT number.	There are no CC-486 solid tumor clinical trials that may potentially transition subjects into the CC-486-GEN-001 study.
Medical Monitor / Emergency Contact Information	Updated contact details for the Medical Monitor and 24-hour Emergency Phone Number	Administrative change.
Celgene Therapeutic Area Head Signature Page	Therapeutic Area Head and title were updated.	Administrative change.
Section 1.1.1, Acute Myeloid Leukemia	Updated background information and references for disease background of acute myeloid leukemia.	Information was updated based on recent publications.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 1.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 1.1.3, Solid Tumor Pathogenesis	Section was deleted.	There are no CC-486 solid tumors clinical trials that may potentially transition subjects into CC-486-GEN-001 study.
Section 1.2.1, CC-486 (Oral Azacitidine)	Provided updated compound background information for CC-486 (oral azacitidine).	Information was updated based on the most recent version of the IB.
Section 1.3.1, Study Rationale and Purpose Section 3.1, Study Design	Deleted a part of the sentence regarding subjects with solid malignancies as this study will not include that population.	There are no CC-486 solid tumor clinical trials that may potentially transition subjects into the CC-486-GEN-001 study.
Section 1.4, Benefit/Risk Assessment Section 1.4.1, Risk Assessment Section 1.4.2, Benefit Assessment Section 1.4.3, Overall Benefit/Risk Assessment	New sections and table added.	To incorporate stand-alone risk/ benefit assessment information into the protocol.
Table 3, Study Endpoints	Changed wording from “study termination” to “End of Trial”.	Minor wording change for clarity.
Section 3.3, End of Trial	Added 2 new criteria for End of Trial: 1. The date of the study termination by the Sponsor 2. The date of the last per-protocol visit for subjects who are transferred to commercially available and/or reimbursed CC-486 in the participating countries where CC-486 is approved by regulatory authorities for the indication that the subject is being treated.	Updated for inclusiveness and accuracy.
Section 4.2, Inclusion Criteria Section 10.4.1, Pregnancy Appendix C, Females of Childbearing Potential Definitions and Methods of Contraception	Contraceptive requirements have been updated and new appendix added.	As per IB, CC-486 has been found in pre-clinical studies to be both teratogenic and fetotoxic. Therefore, inclusion criterion 4 has been modified based on Clinical Trials Facilitation and Coordination Group last US Food and Drug Administration (FDA) guidance for compounds that are found to be teratogenic/fetotoxic.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 1.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 4: Table of Events	Updated footnote related to pregnancy testing in the table of events.	The information for pregnancy testing has been moved from Section 6.1.7 to Appendix C.
Section 6.1.7, Pregnancy Testing (Females of Childbearing Potential [FCBP] Only) and Contraception Education	The section has been deleted from the body of the protocol and following section numbers updated.	The information has been moved from the body of the protocol to Appendix C.
Section 6.2.1, Cycle 1 Procedures/Assessments	Added statement that unscheduled visits may be performed if deemed necessary by the Investigator.	An additional clarification to the study procedures was added.
Section 6.3.2, Survival Follow-up or Long-term Follow-up	Updated end of trial criteria.	For internal consistency with the end of trial criteria in the other sections of the protocol.
Section 7.1, Description of Investigational Product	Added a 300-mg tablet option to the list.	To align with the current version of CC-486 product information.
Section 7.2.3, Investigational Product Administration	Administration and ingestion of oral azacitidine tablets have been updated.	Information was updated based on most recent version of the IB.
Section 7.2.4, Missing Doses	More information regarding missed doses has been added.	Information was updated based on most recent version of the IB.
Section 7.2.6, Dose Modifications	Removed the option for 600 mg/day to 500 mg/day.	There are no studies with a 600-mg exposure that would roll over into this protocol.
Table 5, Criteria for Interrupting or Resuming Study Treatment	Revised criteria for interrupting or resuming Study Treatment.	Information was updated based on most recent version of the IB.
Section 8.1, Permitted Concomitant Medications and Procedures	Parenteral flu vaccinations are permitted, and information regarding coronavirus 2019 (COVID-19) vaccinations has also been added.	Clarification added in the context of viral infections risk (including COVID-19 pandemic).
Section 8.2: Prohibited Concomitant Medications and Procedures	Drug-drug interactions have not been studied with CC-486, and live COVID-19 vaccines should generally not be administered to a participant during the study.	Information was updated based on most recent version of the IB. Clarification added in the context of COVID-19 pandemic risk.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 1.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.1, Overview	The 2 following sentences were removed: "In addition, where appropriate, a total column will be included to summarize subjects across treatment regimens". "All statistical analyses specified in this protocol will be conducted using SAS® Version 9.2 or higher unless otherwise specified".	Information updated considering the sample size based on number of subjects in parent CC-486 studies. The statistical analysis will be provided in the statistical analysis plan (SAP).
Section 9.3, Sample Size and Power Considerations	Deleted prior section of efficacy evaluable population. Minor rewording of the sample size.	Information updated considering the sample size based on number of subjects in ongoing parent CC-486 studies. The statistical analysis will be provided in the SAP.
Section 9.5, Subject Disposition	Removed the sentence "A summary of subjects enrolled by site will be provided." This information will be moved to the statistical analysis plan (SAP).	Updated as information will be found in the SAP.
Section 9.6, Overall Survival	Removed previous section of Efficacy Analysis. Specified that overall survival (OS) analysis will be performed for subjects if the sample size and number of deaths allows for meaningful results.	Efficacy analysis to be performed in the parent CC-486 studies. Only OS analysis may be performed depending on sample size. The statistical analysis will be provided in the SAP.
Section 9.7, Safety Analysis	Revised statement so that safety analysis will be performed on subjects who meet the safety population definition.	Definition of safety population is provided in Section 9.2.2.
Section 10.1, Monitoring, Recording, and Reporting of Adverse Events	Adverse events of special interest will be collected if applicable and required from the parent CC-486 study. Adverse events (AEs) that occur after consent related to COVID-19 must be reported.	Clarification added in the context of requirements of parent CC-486 studies. Clarification added in the context of COVID-19 pandemic risk.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 1.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 10.1, Monitoring, Recording, and Reporting of Adverse Events Section 10.2.1, Seriousness Section 10.4.1, Females of Childbearing Potential Section 10.5, Reporting of Serious Adverse Events Section 10.5.1, Safety Queries Section 10.6, Expedited Reporting of Adverse Events	Updates to adverse event reporting have been added.	Updated information regarding AE reporting.
Section 11.2, Study Discontinuation	Added new criteria for study discontinuation.	Added new criteria for overall comprehensiveness.
Section 13.9, Sponsor Commitment to Diversity in Clinical Trials	Added a new section to align with Sponsor commitment to diversity in clinical trials.	To align with Sponsor practices and to comply with European Union Clinical Trial Regulation (EU-CTR) requirements.
Section 14.4, Data Protection, Data Privacy, and Data Security	Added a new section regarding data practices.	To align with Sponsor practices and to comply with EU-CTR requirements.

PROTOCOL SUMMARY

Study Title

A Phase 2, Open-label, Single-arm Rollover Study to Evaluate Long-term Safety in Subjects Who Participated in Other Celgene Sponsored CC-486 (oral azacitidine) Clinical Trials in Hematological Disorders.

Indication

Rollover study supporting hematological disorder indications from Celgene-sponsored CC-486 (also known as BMS-986345) protocols eligible for participation in the study.

Objectives

Primary Objectives: To evaluate the long-term safety of CC-486 (oral azacitidine) in subjects who have received CC-486 as monotherapy in other Celgene-sponsored clinical trials and whom the Investigators feel may derive clinical benefit from continuing treatment with CC-486.

Secondary Objectives: To follow subjects treated with CC-486 or placebo (in parent CC-486 study) for survival if required by the parent CC-486 study protocol.

Study Design

The open-label, multicenter, multinational rollover study is intended to evaluate the safety of CC-486, while providing continued treatment with CC-486 for subjects who are receiving single agent CC-486 at the time of transition to the rollover study and tolerated the protocol prescribed regimen in Celgene-sponsored trials, and whom in the opinion of the Investigator may derive clinical benefit from continuing treatment with CC-486.

The study design is described in detail in Section 3.1

The study will be conducted in compliance with International Conference on Harmonisation (ICH) Good Clinical Practices (GCPs).

Study Population

All subjects participating in a Celgene CC-486 sponsored study whether on active CC-486 or placebo, and as described in Section 4 of this protocol may participate in this study.

In order to receive investigational product (IP) in this protocol, subjects must have previously participated in a CC-486 study and who, in the opinion of the Investigator may derive clinical benefit from continuing treatment with CC-486 monotherapy. The subject must not have been discontinued from receiving IP in the parent CC-486 protocol prior to entering this study.

In addition, any subject who had received CC-486 or placebo in a parent CC-486 protocol but had been discontinued from IP and were in survival follow-up in the parent CC-486 study, may be rolled over into this protocol and will continue to be followed for survival as in the parent CC-486 protocol.

In order to enter the survival follow-up in the Follow-up Phase of the rollover study, subjects must have been enrolled into a parent CC-486 study where monitoring for survival is required.

Length of Study

The study will terminate and relevant subjects will discontinue from the study when CC-486 receives regulatory approval in the indication for which they are being treated, and is also commercially available and reimbursed such that the subject's access to CC-486 is neither interrupted nor discontinued by the relevant local healthcare provider.

The End of Trial is defined as the following, whichever is the later date:

- the date of the last visit of the last subject to complete the post-treatment follow-up,
- the date of receipt of the last data point from the last subject that is required for primary and/or secondary analysis, as pre-specified in the protocol,
- the date of the study termination by the Sponsor,
- the date of the last per-protocol visit for subjects who are transferred to commercially available and/or reimbursed CC-486 in the participating countries where CC-486 is approved by regulatory authorities for the indication that subject is being treated.

Study Treatments

Subjects will receive CC-486 during the treatment phase of the study. The dose and schedule of CC-486 in this study will be dictated by the single agent CC-486 dose received at the time of transitioning in the parent CC-486 study, taking into account the subject's last dose and schedule of CC-486 in the parent CC-486 study. In the Celgene-sponsored, placebo-controlled, parent CC-486 studies requiring survival follow-up, subjects who received placebo may transition into this study; however, they will not receive CC-486 treatment. These subjects, with consent, will be followed for survival.

Overview of Survival Follow-up Assessment

Survival data will be collected for subjects transitioning from parent CC-486 studies, if defined in the protocol of the parent CC-486 study.

Overview of Key Safety Assessments

All subjects will be monitored for safety throughout the study. Safety variables include the following:

- Physical examination (PE)
- Vital signs
- Clinical laboratory measurements, including hematology, serum chemistry and pregnancy tests (if applicable)
- Concomitant medications/procedures
- Adverse events (AEs)
- Pregnancy testing (for females of childbearing potential subjects)

During treatment phase of the study, PE, vital signs, and clinical laboratory assessments are performed (these data will be captured in the source documents only). Concomitant medications/procedures and AEs are reported in the clinical case report form database.

All subjects will be monitored for AEs; starting from the time the subject signs the informed consent form until 28 days after the last dose of study treatment.

Statistical Methods

This open-label, single-arm rollover study is designed to evaluate long-term safety in subjects who participated in monotherapy clinical trials of CC-486 (oral azacitidine) in myeloid disorders.

Analysis Populations

The Safety population includes all enrolled subjects who were determined eligible to receive IP in this rollover study. The Safety population will be used for all safety analysis. Subjects will be analyzed according to the treatment actually received.

Sample Size

The size of this study will be defined by the number of subjects rolling over to this study from parent CC-486 studies.

Overall Survival

Overall survival analysis will be performed if it is required by the parent CC-486 protocol, and if the sample size of subjects and number of deaths allow to conduct the appropriate analysis.

Safety Analyses

All subjects in the safety population will be included in the safety analyses. Safety and tolerability will be monitored through continuous reporting of AEs and serious adverse events, deaths, and incidence of subjects experiencing AEs resulting in dose reductions, dose interruptions, and/or premature discontinuation of IP. Adverse events and concomitant medications/procedures will be tabulated and summarized across the study as one group, by treatment regimen, if applicable.

Interim Analysis

There is no interim analysis planned for this study.

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1. INTRODUCTION

1.1. Disease Background

1.1.1. Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is a malignancy of the myeloid precursor cell line, characterized by the rapid proliferation of abnormal cells, which accumulate in the bone marrow and interfere with the production of normal blood cells. Approximately 21,450 people were estimated to have been diagnosed with AML in 2019 in the United States (US) and 10,920 subjects were estimated to have died from the disease (Siegel, 2019). In Europe, the occurrence of newly diagnosed AML is estimated at approximately 18,000 cases annually (Rodriguez-Abreu, 2007). Worldwide, the incidence of AML is highest in the US, Australia, and Western Europe (Redaelli, 2003). Acute myeloid leukemia is mostly a disease of older individuals with a median age of approximately 68 years at diagnosis and median age of 72 years at death (National Cancer Institute, 2019).

AML is generally classified as de novo or secondary when arising following exposure to prior cytotoxic chemotherapy or after a history of prior myelodysplastic syndromes (MDS) or other antecedent hematologic disorder. The pathogenesis of AML at the genetic level is also heterogeneous. Comprehensive profiling of genetic alterations in AML will enhance disease classification, risk stratification, and prognosis, and ultimately allow more precise therapeutic interventions.

It is estimated that 35% to 40% of patients with myelodysplastic syndromes (MDS) will go on to develop AML, and the disease is often refractory to current therapy (Silverman, 2000). Preexisting myelodysplastic or myeloproliferative disorders are common in older patients with AML, occurring in 24% to 40% of cases (Gajewski, 1989). Acute myeloid leukemia patients with antecedent hematologic disease have a lesser response to therapy than those with de novo disease (Gajewski, 1989; Leith, 1997).

Treatment of AML is divided into two phases: induction of remission and post remission therapy. For more than 30 years, the combination of cytarabine and anthracycline has been the mainstay of treatments to induce remission (Löwenberg, 1999; Tallman, 2005). For patients eligible for intensive induction chemotherapy, the combination of cytarabine and anthracycline has been the mainstay of treatments to induce remission (National Comprehensive Cancer Network [NCCN] AML, 2021; Döhner, 2017). First-line induction therapy of cytarabine 100 to 200 mg/m^2 × 7 days followed by either idarubicin 12 mg/m^2 × 3 days or daunorubicin 45 to 90 mg/m^2 × 3 days, referred to as "7+3 protocol," is the backbone of conventional treatment for patients who can tolerate intensive chemotherapy. In patients under 60 years, complete remission (CR) rates can be achieved in 75% to 90% of patients usually with one course of treatment, and the overall 5-year survival is approximately 50% (Burnett, 2005).

Although induction chemotherapy produces morphologic CRs in about 60% to 80% of younger adults and 40% to 50% of older adults with newly-diagnosed AML, there is a substantial population of patients who will fail to attain CR (ie, refractory) (Mangan, 2011). Even for those

who attain CR after induction treatment, a significant portion will eventually relapse, leading to only about 29% relapse-free survival at 3 years (Yanada, 2007).

In elderly patients with AML, defined as older than 60 years, conventional cytotoxic intensive chemotherapy has been associated with CR rates of approximately 45%, without durability and with higher early treatment-related mortality and shorter survival, with a median survival between 7 to 12 months (Dombret, 2008; Jabbour, 2006). Elderly patients with AML have significant comorbidities, an increased frequency of adverse cytogenetic abnormalities, performance status, a higher incidence of AML arising from MDS, and resistance to conventional treatments. For these reasons, elderly patients may not be candidates for standard intensive induction chemotherapy regimens (DiNardo, 2019; Pettit, 2015).

Patients considered ineligible for intensive induction chemotherapy are generally patients older than 75 years of age or those 60 to 75 years old with significant comorbidities, poor performance status, or with complex cytogenetic abnormalities (DiNardo, 2019; Milligan, 2006; Pettit, 2015; Tallman, 2019). Treatment options for patients who are not candidates for intensive induction chemotherapy and who do not have actionable mutations include: low-intensity therapies, such as low-dose cytarabine (LDAC), hypomethylating agents (HMAs; azacitidine or decitabine), supportive care only, glasdegib in combination with LDAC, or the venetoclax combination regimens with HMAs or LDAC (Kucukyurt, 2019; LeBlanc, 2019; Tallman, 2019).

Current approaches to post remission therapy include consolidation chemotherapy, hematopoietic stem cell transplant (HSCT) and maintenance therapy.

1.1.2. Myelodysplastic Syndromes

Myelodysplastic syndromes encompass heterogeneous collection of hematopoietic stem cell disorders primarily affecting older adults. Myelodysplastic syndromes are typically characterized by bone marrow hyperplasia and peripheral cytopenias that manifest clinically as anemia, neutropenia and/or thrombocytopenia of variable frequency and severity. Anemia is the most frequent laboratory finding and it often progresses to red blood cell (RBC) transfusion dependence. Other less common presenting clinical features related to the cytopenias are an increased risk of infection and/or hemorrhage, and a potential to progress to AML (Catenacci, 2005). It is estimated that 5 cases per 100,000 persons per year are diagnosed with MDS (NCCN, 2015). The elderly are particularly vulnerable with annual incidence rates between 26 and 48 cases per 100,000 persons per year (NCCN, 2015).

Myelodysplastic syndromes are classified according to World Health Organization (WHO) criteria by pathologic features on bone marrow examination (Vardiman, 2009). Myelodysplastic syndromes are also categorized into one of 4 risk groups (Low, Intermediate-1 [INT-1], Intermediate-2 [INT-2], and High risk) according to the International Prognostic Scoring System (IPSS) based on cytogenetic features, number of cytopenias and bone marrow blast percentages (Greenberg, 1997). Overall survival and risk of progression to AML is significantly different in the 4 risk groups (Greenberg, 1997). The Low and INT-1 groups tend to have a better prognosis than do subjects with INT-2 or High risk disease, with the median survival for patients in these risk groups being 5.7 years (Low), 3.5 years (INT-1), 1.2 years (INT-2) and 0.4 years (High)

(Greenberg, 1997). The median time for 25% of patients to progress to AML is 9.4, 3.3, 1.1, and 0.2 years, respectively, in the Low, INT-1, INT-2 and High risk groups (Greenberg, 1997).

The mainstay of therapy in IPSS lower-risk (Low or INT-1 risk) MDS has been supportive care, which includes the use of RBC and/or platelet transfusions, treatment of infections, and the use of erythropoiesis stimulating agents (ESAs) such as epoetin alfa or darbepoietin, plus hematopoietic growth factors such as granulocyte colony-stimulating factor (G-CSF) when needed (Silverman, 2000). As the outcome of patients with lower-risk MDS is not improved by early introduction of allogeneic hematopoietic stem cell transplantation (HSCT) (Cutler, 2010), allogeneic HSCT is recommended at the time of disease progression for lower-risk MDS patients (NCCN, 2015).

1.2. Compound Background

1.2.1. CC-486 (Oral Azacitidine)

Azacitidine is an analog of the naturally occurring pyrimidine nucleoside cytidine and is classified as an antimetabolite.

Azacitidine injectable is marketed worldwide under the trade name Vidaza® (azacitidine for injection). Azacitidine injectable was first approved in the US on 19 May 2004 for the following 5 subtypes of myelodysplastic syndrome (MDS) per the French American-British classification system: refractory anemia (RA) or RA with ringed sideroblasts (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), RA with excess blasts (RAEB), RAEB in transformation, and chronic myelomonocytic leukemia (CMML). Azacitidine injectable is approved in the US for both subcutaneous (SC) and intravenous (IV) routes of administration. Azacitidine (SC use only) was approved in the European Union (EU) on 17-Dec-2008 for the treatment of adult patients who are not eligible for hematopoietic stem cell transplantation (HSCT) with intermediate-2 (INT-2) and high-risk MDS according to the IPSS, CMML with 10% to 29% marrow blasts without myeloproliferative disorder, and AML with 20% to 30% blasts and multilineage dysplasia, according to the World Health Organization (WHO) classification. In addition, the following indication of AML with > 30% marrow blasts, according to the WHO classification, was added and revised by the European Commission decisions adopted on 28-Oct-2015 and 29-Jun-2016, accordingly. As of 18-Jan-2022, azacitidine injectable is approved in 85 countries, including the US and EU. Depending on the country, azacitidine injectable is approved for SC use only or for both SC and IV administration.

Azacitidine has also been formulated for oral administration. CC-486 (ONUREG, oral azacitidine), also known as BMS-986345, is approved in many regions including the United States (US), Canada, European Union (EU), and United Kingdom for continued treatment of adult patients with AML 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 (ONUREG® USPI, 2020). Oral azacitidine was approved in Canada on 05-Jan-2021 for maintenance therapy in adult patients with AML who achieved CR or CRi following induction therapy with or without consolidation treatment, and who are not eligible for HSCT. On 17-Jun-2021, the ethics committee (EC) granted the Marketing Authorization for ONUREG for maintenance therapy in adult patients with AML who achieved

CR or CRi following induction therapy with or without consolidation treatment, and who are not candidates for, including those who choose not to proceed to, HSCT.

CC-486 is being developed and is currently being evaluated in clinical trials, either as a single agent or in combination with other drugs for the treatment of hematological malignancies. The oral formulation provides an opportunity for a more convenient home administration than the hospital/clinic setting.

Azacitidine has strong in vitro and in vivo antileukemic activity at cytotoxic concentrations and the ability to induce differentiation at lower concentrations in hematopoietic and non-hematopoietic cell lines. The cytotoxic effects of azacitidine may result from multiple mechanisms, including inhibition of DNA, RNA and protein synthesis, incorporation into RNA and DNA, and activation of DNA damage pathways. The ability of azacitidine to cause differentiation can be attributed to its activity as a hypomethylating agent. The degree of methylation of cytosine residues in DNA has been demonstrated to play a role in gene expression. Indeed, cytosine hypermethylation of the genes critical to ensure orderly cell proliferation and maturation (differentiation) is frequently found in primary neoplasms and tumor cell lines (Zingg, 1997). Therefore, use of an inhibitor of DNA methylation, such as azacitidine, would be a rational approach for the treatment of various malignancies including AML, MDS and CMML to revert these epigenetic aberrations in the malignant clone and to re-establish the antiproliferative signals that were extinguished by hypermethylation. Recent data (Tsai, 2012) support the concept that DNA hypomethylating agents at low doses can reprogram the aberrant epigenetic state of cancer cells to elicit sustained antitumor activity. Preliminary data from the AZA-PH-GL-2003-CL-001 survival study with Vidaza in higher-risk MDS patients found from an analysis of pretreatment bone marrow methylation density that the overall survival (OS) benefit observed with azacitidine versus the conventional care regimen (CCR) was independent of methylation status of the 5 genes analyzed (CDKN2B [p15], SOCS1, CDH1 [E-cadherin], TP73, and CTNNA1 [α-catenin]). However, increasing methylation was associated with worse OS and patients with lower levels of methylation treated with azacitidine had the best OS, suggesting they may derive greater benefit from azacitidine.

Parenteral azacitidine has been extensively studied in MDS and AML. In MDS it has been shown in a large, randomized Phase 3 trial of higher-risk MDS patients to provide a survival advantage of 9.4 months over CCRs and thus altering the natural course of MDS. The median OS of azacitidine-treated patients was 24.5 months compared with 15.0 months for the combined CCR group, which included best supportive care (BSC), low-dose cytarabine, and intensive chemotherapy (Fenaux, 2009). The clinical experience of azacitidine in AML is smaller, but positive efficacy results have been obtained. In a subset of 113 patients with WHO-defined AML (mean age 70 years, 24% with unfavorable karyotype, median bone marrow blasts 23%) from the larger MDS study discussed above, the median OS was 24.5 months (n = 55) in the azacitidine arm compared with 15.0 months (n = 58) in the CCR (Fenaux, 2008; Fenaux, 2009). Additionally, the outcome was not significantly different in patients with unfavorable karyotypes, although the sample size was small. Silverman et al, using WHO AML criteria for diagnosis, reported a median OS of 19.3 months (n = 27) in azacitidine treated patients compared with 12.9 months (n = 25) in

patients who received BSC (Silverman, 2006). Additionally, Goldberg et al reported on 33 patients who received azacitidine (n = 11, median age 74) or 7 + 3 intensive chemotherapy (n = 22, median age 67 years). Median blast counts at baseline were 42% in the azacitidine group and 65% in the intensive chemotherapy group. The median OS was 13.2 months in azacitidine-treated patients compared with 9.2 months in intensive chemotherapy patients (Goldberg, 2006). All of the above mentioned studies used the standard azacitidine dose of 75 mg/m^2/day for 7 days.

An oral formulation of azacitidine (CC-486) entered clinical testing in 2006 in subjects with MDS, CMML, and AML. The AZA PH US 2007 CL 005 study has shown that CC-486 is bioavailable and produces cumulative exposures (area under the concentration curve [AUC]) that are 30% to 60% of the exposure achieved with the labeled dose and schedule of Vidaza. A maximum tolerated dose (MTD) of 480 mg daily for 7 days was defined based on dose-limiting diarrhea at 600 mg (Garcia-Manero, 2011). As expected, reversible and manageable myelosuppression was also observed. Pharmacodynamic activity (DNA hypomethylation) and clinical responses were observed with CC-486, although the cross-over design (with SC Vidaza administered during Cycle 1), confounded the interpretation of these responses in Part 1 of the study.

The second part of the AZA PH US 2007 CL 005 study went on to explore both daily and twice-daily extended dosing schedules of 14 and 21 out of 28 days in a non-crossover fashion. Daily doses of 300 mg have proven to be tolerated on both the 14 and 21 out of 28-day schedules with myelosuppression, gastrointestinal symptoms, and fatigue being the most common toxicities (Garcia-Manero, 2011).

In the AZA PH US 2007 CL 005 study, DNA methylation levels in blood were measured as a pharmacodynamic endpoint, to determine DNA hypomethylating activity of CC-486. In Part 1 of the study, CC-486 administration for the first 7 days of a 28-day cycle reduced DNA methylation in the blood, with maximum hypomethylation achieved on Day 15 (8 days after the last dose), and methylation levels returned to near-baseline values by the end of cycle. In Part 2 of the study, DNA methylation levels in blood were measured to determine the DNA hypomethylating activity of CC-486 when administered orally at 300 mg once daily (QD) for 14 or 21 days of 28-day cycles. Subjects treated with CC-486 for 21 days had DNA hypomethylation that persisted through the end of cycle. This contrasts with the lack of persistent hypomethylation at the end of cycle when treated with CC-486 for only 7 days, thus providing mechanistic support for treating beyond 7 days. In summary, CC-486 is biologically active, reducing DNA methylation when administered at low doses on extended schedules.

The primary analysis of a controlled Phase 3 study assessing the efficacy of CC-486 to treat subjects with IPSS lower-risk MDS (AZA-MDS-003) has been completed. Subjects were randomized 1:1 to receive 300 mg CC-486 or placebo QD for the first 21 days of each 28-day treatment cycle. The primary efficacy endpoint of red blood cell (RBC) transfusion independence with a duration of 56 days (8 weeks) or longer in subjects with IPSS lower-risk MDS with RBC transfusion-dependent anemia and thrombocytopenia was achieved in 31% of subjects treated with CC-486 (n = 107) compared to 12% of subjects treated with placebo (n = 109), with a statistically significant difference of almost 19% (p = 0.0005). The median duration of RBC transfusion independence for subjects treated with CC-486 was 11.1 months with a median onset of

2.4 months. In addition, subjects treated with CC-486 demonstrated significant clinical benefit across multiple other parameters measured, namely, hematologic improvement–erythroid response (10.9% rate difference, CC-486 group over placebo group), hematologic improvement-platelet response (17.0% rate difference, CC-486 group over placebo group), hemoglobin increase, and increase in platelet counts. Approximately 50% fewer subjects experienced progression to AML in the CC-486 group compared to the placebo group. Overall survival was assessed as an interim analysis at the time of the primary analysis and demonstrated no significant or clinically meaningful difference in survival between the 2 treatment groups with a hazard ratio (HR) 1.03 (p = 0.8759) (Garcia-Manero, 2021).

The efficacy of CC-486 as a maintenance therapy in subjects with AML aged 55 years or older who were in remission following induction/consolidation therapy and were not eligible for HSCT was assessed in a controlled Phase 3 study (CC-486-AML-001). Results of the primary analysis were positive; the primary efficacy endpoint of OS and the key secondary efficacy endpoint of relapse-free survival (RFS) were both significantly improved in the CC-486 group (stratified log-rank test p = 0.0009 for OS and p = 0.0001 for RFS). Treatment with CC-486 (n = 238) resulted in a median OS of 24.7 months, a clinically meaningful increase of 9.9 months over placebo (14.8 months), and a 31% reduction in the risk of death. The median RFS was 10.2 months for the CC-486 group and 4.8 months for the placebo group, with a clinically meaningful difference in median RFS of 5.3 months with CC-486 treatment. The stratified HR was 0.65 (95% confidence interval: 0.52, 0.81), indicating a 35% reduction in risk of relapse or death for the CC-486 group, which demonstrated the benefit of CC-486 as maintenance therapy for the treatment of AML. CC-486 was associated with significantly lower rates of hospitalization events compared to placebo (0.48 events per person-year for the CC-486 group and 0.64 events per person-year for the placebo group [nominal p = 0.0068]) and number of days hospitalized (7.89 days per person year for CC-486 compared to 13.36 days per person-year for placebo, nominal p < 0.0001) (Wei, 2020).

Please refer to the Investigator's Brochure for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of the investigational product (IP).

1.3. Rationale

1.3.1. Study Rationale and Purpose

The proposed open-label, multicenter, multinational rollover study is intended to evaluate the long-term safety of CC-486, while providing continued treatment with CC-486 for subjects who received single agent CC-486 in Celgene-sponsored trials, and who in the opinion of the Investigator may derive clinical benefit from continuing treatment with CC-486.

CC-486 provides an opportunity to deliver azacitidine at lower systemic doses over a more prolonged schedule than can be practically achieved with parenteral therapy. In addition, CC-486 can be taken at home rather than in the hospital/clinic setting representing an opportunity for patients with various hematological malignancies including AML and MDS, under adequate control or in remission and may offer better quality of life and possibly a survival advantage.

1.3.2. Rationale for the Study Design

This open-label, multicenter, non-randomized study is designed to evaluate long-term safety of CC-486 and at the same time provides continued access to CC-486 for eligible subjects who were previously enrolled and treated with single agent CC-486 in a parent CC-486 protocol and did not meet the criteria for discontinuation described in the parent CC-486 study protocol, and are still deriving clinical benefit (as assessed by Investigator). These subjects may therefore potentially benefit from continued treatment with CC-486. In this study subjects will initiate treatment with CC-486 at the dose and schedule of the last visit of the parent CC-486 study. Treatment will continue until progression of disease or disease relapse or as long as the subject is deriving clinical benefit, as judged by the Investigator, or upon commercial availability of CC-486 for the indication in the participating country.

1.4 Benefit/Risk Assessment

Detailed information about the known and expected benefits and risks and reasonably anticipated AEs of CC-486 can be found in the Investigator's Brochure.

1.4.1 Risk Assessment

Table 1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s)		
The known risks associated with CC-486 treatment classified as very common (a 10% or more chance that this will happen) include neutropenia, leukopenia, febrile neutropenia, thrombocytopenia, infections (including pneumonia or infections of the upper respiratory tract), nausea, vomiting, diarrhea, abdominal or upper abdominal pain, constipation, asthenia, fatigue, pyrexia, decreased appetite, weight decreased, and pain (including arthralgia, back pain, pain in extremity).	The reported AEs in global study oral azacitidine AZA-MDS-003 were consistent with the known safety profile of azacitidine. There were no new safety signals or unexpected safety findings observed with the oral azacitidine regimen.	The proposed safety monitoring (Section 10.1), and toxicity management guidance (Table 5) will minimize the risks for the subjects in this study.
Study Procedures		
There are no study-specific procedures that have been identified as potential risks to subjects of this study.	N/A	N/A

Table 1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Other		
The COVID-19 pandemic has been identified as a potential risk to clinical study subjects in general.	It is not known whether taking CC-486 increases the risk of SARS-CoV-2 infection or the duration or severity of COVID-19.	The study has been designed with study visits that allow for close monitoring of the subjects' safety throughout the clinical study (Table 4, Section 6), and unscheduled visits may be performed if clinically indicated (Section 6). To facilitate enhanced reporting of COVID-19 events that occur during the study, all AEs and SAEs reported after the time of consent that are related to SARS-CoV-2 or COVID-19 infection must be reported (Section 10.1). Individual benefit-risk considerations remain the responsibility of the Investigator. Investigators should apply clinical judgment, and these risks should be considered when enrolling a participant.

Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 2019; N/A = not applicable; SAE = serious adverse events; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

1.4.2 Benefit Assessment

Oral azacitidine is the first therapy used in the maintenance setting to provide statistically significant and clinically meaningful improvements in both OS and recurrence-free survival (RFS) in patients with AML in remission following induction chemotherapy with or without consolidation. Oral CC-486 has a manageable safety profile and represents a new therapeutic standard for patients with AML in remission (Wei, 2019).

Oral azacitidine has demonstrated a clinical benefit in MDS subjects with a decreased risk of progression to AML and a potential correction of the peripheral blood cytopenias, including the correction of packed red blood cells (pRBCs) or platelet transfusion dependence. While a benefit of overall survival has not been demonstrated by using CC-486, it can elicit pRBC transfusion independence in heavily pre-transfused MDS patients.

Therefore, the development of CC-486 offers an oral alternative to conventional HMA (including injectable azacitidine) and provides a treatment option for patients with AML and those patients with MDS who have exhausted symptomatic treatments and are in need for a disease-modifying treatment. The oral formulation provides an opportunity for a more convenient home administration than the injectable azacitidine that requires the hospital/clinic setting.

1.4.3 Overall Benefit/Risk Conclusion

Taking into account the measures to minimize risk to subjects in this study, the potential risks identified in association with oral azacitidine are justified by the anticipated benefits that may be afforded to subjects with myeloid disorders. The Sponsor will evaluate the benefit/risk profile of the study on an ongoing basis. This evaluation will be based on all available data with particular attention to AEs or other safety trends in this or any other clinical study of CC-486 whose nature, severity, and/or frequency suggest that subjects would be exposed to an unreasonable and significant risk of illness or injury; and new nonclinical data which suggest unreasonable and significant risk of illness or injury. If such evaluation suggests that the risk/benefit profile of the study has become unfavorable to subjects, the Sponsor will pause enrollment and/or treatment until further evaluation of data, and interaction with the appropriate Health Authority(ies) can take place on potential actions. Such actions may include (but are not limited to) study continuation, substantial amendment, or termination of the study. However, no available safety information has been identified which would alter the currently known benefit/risk profile for azacitidine.

2. STUDY OBJECTIVES AND ENDPOINTS

Table 2: Study Objectives

Primary Objective
The primary objective of the study is to evaluate the long-term safety of CC-486 (oral azacitidine) in subjects who have received CC-486 as monotherapy in other Celgene-sponsored clinical trials and whom the Investigators feel may derive clinical benefit from continuing treatment with CC-486.
Secondary Objective(s)
The secondary objective is to follow subjects treated with CC-486 or placebo (in parent CC-486 study) for survival if required by the parent CC-486 study protocol.
Exploratory Objective(s)
None.

Table 3: Study Endpoints

Endpoint	Name	Description	Timeframe
Primary	Safety	Type, frequency, severity and relationship of treatment emergent adverse events to investigational product	At End of Trial
Secondary	Survival	Time from randomization until death from any cause	At End of Trial
Exploratory	None		

3. OVERALL STUDY DESIGN

3.1. Study Design

The open-label, multicenter, multinational rollover study is intended to evaluate the long-term safety of CC-486, while providing continued treatment with CC-486 for subjects who are receiving single agent CC-486 at the time of transition to rollover study and tolerated the protocol prescribed regimen in Celgene-sponsored trials, and who, in the opinion of the Investigator, may derive clinical benefit from continuing treatment with CC-486. Subjects' survival will also be followed if required by the parent CC-486 study protocol. If approved by Celgene, subjects from any ongoing or future Celgene sponsored CC-486 studies in hematological disorders will be included in this protocol.

The overall study design is described in Figure 1.

3.1.1. Study Entry/Screening Assessment Phase

Once a subject gives written consent, the subject may enter the Study Entry/Screening Assessment Phase. During this period, the subject will undergo safety and other assessments to reconfirm eligibility for the study. Assessments conducted during the End of Study visit in the parent CC-486 study may be used if these are the same assessments specified in this rollover protocol and fall within the required timeframe. Once the subject has fulfilled the required assessment in the Study Entry/Screening Assessment Phase, the subject will enter the Treatment Period.

To ensure no gaps in IP dosing, subjects should start study entry/screening assessment procedures within 7 days of the End of Study visit from their parent CC-486 study. Ideally, Day 1 of the first cycle in the rollover study should occur on the same day as the End of Study visit from the parent CC-486 study. A subject's transition into the rollover study should not exceed more than 45 days after the End of Study visit of the parent CC-486 study.

Assessments performed as part of the End of Study visit from parent CC-486 study do not need to be repeated on Day 1 of the rollover study if performed within 7 days.

Please refer to Section 6.1 and Table 4 for all assessments to be performed during the Study Entry/Screening Assessment Phase.

3.1.2. Treatment Phase

Subjects who meet all inclusion and none of the exclusion criteria will be evaluated at the clinic on the intended Day 1 (ie, predose) for study entry/screening assessments.

The dose and schedule of CC-486 in this study will be dictated by which parent CC-486 study the subject participated in, taking into account their last single agent dose and schedule of CC-486 in the parent CC-486 study. For some subjects, a formulation change of the IP from capsule formulation to tablet formulation must occur after enrolling into this rollover study.

Safety will be monitored throughout the study from the time informed consent is obtained until 28 days after the last dose of CC-486.

Subjects will continue participation in this rollover protocol until disease relapse or progressive disease is documented, until a withdrawal criterion (Section 11) is met, or until CC-486 is

commercially available in the participating country for the indication that the subject is being treated. Only subjects whose parent CC-486 studies require follow-up for survival, will be followed for overall survival.

If a subject discontinues from the study for any reason, the subject must undergo the required safety follow-up procedures/assessments as described in Table 4 after the decision to permanently discontinue treatment.

Subjects who received placebo in the randomized parent CC-486 clinical trials will not receive CC-486 treatment. Once consented, these subjects will directly enter survival follow-up in the Follow-up Phase of the rollover study.

3.1.3. Follow-up Phase

All subjects who received CC-486 in this protocol, and discontinue from the Treatment Phase, will enter safety follow-up in the Follow-up Phase of the study. These subjects will be followed for 28 days after the last dose of IP for the assessment of safety related parameters and adverse event (AE) reporting, as well as serious adverse events (SAEs) made known to the Investigator at any time thereafter that are suspected of being related to IP.

Subjects whose parent CC-486 studies require follow-up for survival will be followed for overall survival in this study. Subjects who received placebo in the randomized parent CC-486 clinical trials may transition into the rollover protocol; however, they will not receive CC-486 treatment. Once consented, these subjects will directly enter survival follow-up in the Follow-up Phase of the rollover study.

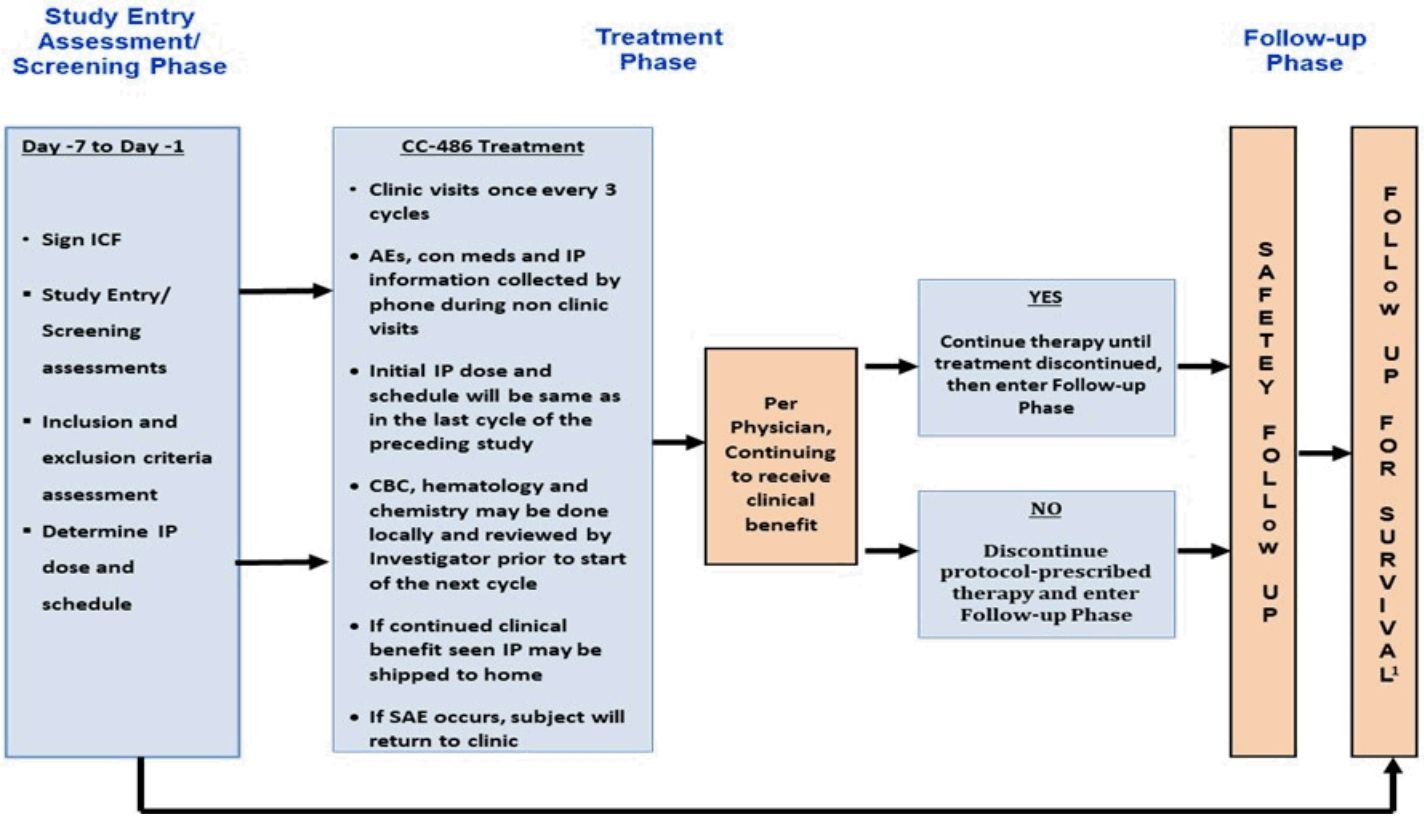
Additionally, all subjects, regardless of treatment with single agent CC-486 or placebo, who discontinued from the treatment phase but are continuing in the follow-up phase of the parent CC-486 study, will also be followed for survival in the rollover study. Once consented, these subjects will directly enter survival follow-up in the Follow-up Phase of the rollover study.

During the follow-up phase of the study, subjects will be followed for survival every month for the first year and then every 3 months until death, withdrawal of consent for further follow-up, study termination, or until a subject is lost to follow-up, according to the parent CC-486 protocol requirements. New anticancer therapies should be collected at the same time schedule.

Survival/long-term follow-up may be conducted by record review (including public records) and/or telephone contact with the subject, family, or the subject's treating physician.

The study will be conducted in compliance with the International Council on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

Figure 1: Overall Study Design



AE = adverse event; CBC = complete blood count; ICF = informed consent form; IP = investigational product; SAE = serious adverse event.

[1] Follow-up for Survival is for subjects indicated. Follow-up for survival will not have the Safety Follow-up.

3.2. Study Duration for Subjects

Subjects will continue to receive IP in this rollover study until disease relapse, documented disease progression, unacceptable toxicity; death, withdrawal of consent, or until study termination. Subjects transitioning from parent CC-486 studies with survival follow-up will require survival follow-up in this rollover study. Subjects who discontinue CC-486 due to an AE will be followed until resolution of the AE or return to baseline.

If the subject discontinues from study treatment for any reason, the subject must undergo the required assessments as soon as possible after the decision to permanently discontinue treatment. Subjects may also be discontinued from the study if CC-486 becomes commercially available in the participating countries for the indications for which subjects are being treated.

3.3. End of Trial

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, the date of receipt of the last data point from the last subject that is required for primary and/or secondary endpoint analysis, as pre-specified in the protocol, the date of the study termination by the Sponsor, or the date of the last per-protocol visit for subjects who are transferred to commercially available and/or reimbursed CC-486 in the participating countries where CC-486 is approved by regulatory authorities for the indication that the subject is being treated, whichever is the later date.

The study will close once CC-486 becomes commercially available in the participating countries for the indications that the subjects are being treated and reimbursed such that the subject's access to CC-486 is neither interrupted nor discontinued by the relevant local healthcare provider.

4. STUDY POPULATION

4.1. Number of Subjects

The total number of subjects and sites cannot be clearly determined or estimated as the number of studies from which subjects will roll over into the present study is not yet known. Subjects who received or will be receiving single agent CC-486 from any ongoing or future CC-486 studies selected by Celgene Corporation may be included in this protocol.

4.2. Inclusion Criteria

Subjects must satisfy the following criteria to be given IP in the study:

1. Previously participated in, and received CC-486, and continues to fulfill the eligibility criteria in one of the parent CC-486 clinical trials.

   The Investigator believes the subject is tolerating treatment with CC-486 monotherapy and continued CC-486 treatment is of benefit to the subject.
2. Understand and voluntarily sign an informed consent document prior to any study-related assessments or procedures being conducted.
3. Willing and able to adhere to the study visit schedule and other protocol requirements.

4. Reproductive Status

- Investigators shall counsel females of childbearing potential (FCBP) (as defined in Appendix C) and male subjects who are sexually active with FCBP, on the importance of pregnancy prevention, the implications of an unexpected pregnancy, and the potential of fetal toxicity occurring due to transmission of study intervention, present in seminal fluid, to a developing fetus, even if the participant has undergone a successful vasectomy or if the partner is pregnant.
- The investigator shall evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
- Local laws and regulations may require the use of alternative and/or additional contraception methods.
- Both male and female subjects must use an efficient method of contraception throughout the transition time frame after the last dose of CC-486 in the parent CC-486 study and prior to the first dose of CC-486 in this study without interruption. Once the subject is in the new study, contraception will be continued throughout participation in the new study and for a period after treatment completion (at the specified time frames for women and men, respectively).
  a) Female Subjects:
     i) Female subjects must have documented proof that they are not of childbearing potential.
        (1) Females who are not of childbearing potential are exempt from contraceptive requirements.
     ii) Females of childbearing potential may participate, provided that the subject meets the following conditions:
        (1) Have two negative pregnancy tests as verified by the investigator prior to starting study treatment. She must agree to ongoing pregnancy testing during the course of the study, and after end of study treatment. This applies even if the subject practices true abstinence from heterosexual contact.
        (2) Either commit to true abstinence from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agree to use and be able to comply with highly effective contraception without interruption, during screening, during the study treatment (including dose interruptions), and for 6 months after discontinuation of study treatment, or longer if required for each compound and/or by local regulations.
  b) Male Subjects:

     Males who are sexually active with FCBP must agree to follow instructions for method(s) of contraception as described below and included in the informed consent form (ICF).
     i) Azoospermic males are not exempt from contraceptive requirements and will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with FCBP, even if the subject has undergone a successful vasectomy or if the partner is pregnant.
     ii) Male subjects are required to use a condom during the intervention period and for at least 90 days after the last dose of study intervention.

iii) Female partners of male subjects should be advised to use a highly effective method of contraception during the study intervention period and for at least 90 days after the last dose of study intervention for the male participant.

iv) Male subjects with a pregnant or breastfeeding partner must agree to remain abstinent from sexual activity or use a male condom during any sexual activity (eg, vaginal, anal, oral) during the intervention period and for at least 90 days after the last dose of study intervention.

v) Male subjects must refrain from donating sperm during the intervention period and for at least 90 days after the last dose of study intervention.

vi) Breastfeeding partners of male subjects should be advised to consult their health care provider about using appropriate highly effective contraception during the time the male participant is required to use condoms.

Subjects must satisfy the following criteria to participate in the Survival Follow-up phase:

1. In order to be enrolled for the survival follow-up in the Follow-up Phase of the rollover study, subjects must have been in a parent CC-486 study where monitoring for survival was required and have signed informed consent for follow-up phase.
2. Understand and voluntarily sign an informed consent document for this study (CC-486-GEN-001).
3. Willing and able to adhere to the study visit schedule and other protocol requirements.

4.3. Exclusion Criteria

The presence of any of the following will exclude a subject from receiving IP in the study:

1. Concomitant use of drugs that are prohibited (listed in the protocol).
2. Prior chemotherapy (including injectable azacitidine) or radiotherapy or any investigational agent after the last dose of CC-486 administered as part of the parent CC-486 study.
3. Subjects have met one or more criteria for discontinuation as stipulated in the parent CC-486 study.
4. Subjects received CC-486 in combination with another compound during a parent CC-486 study (Subjects form multi-arm parent CC-486 studies will be allowed to enroll into the rollover study, if the subject is receiving single-agent CC-486 at the time of transition into the rollover study).
5. A subject's transition into rollover study ≥ 45 days after End of the Study visit of the parent CC-486 study
6. Pregnant or lactating females.

There are no exclusion criteria to prevent entry or remaining on the follow-up phase of this study.

5. TABLE OF EVENTS

Table 4: Table of Events

Events	Study Entry/Screening Assessments Phase	Treatment Phase [a]				Follow-up Phase [a]	
	Day -21 to Day -1	Cycle 1 Day 1	Day 1 of Each Subsequent Cycle (if clinic visit)	Non-clinic Visits (prior to starting subsequent cycles)[b]	End of Treatment	Safety Follow-up [c]	Survival Follow-up
Sign Informed Consent	X	-	-	-	-	-	-
Inclusion/Exclusion Criteria	X	-	-	-	-	-	-
Demographics [d]	X	-	-	-	-	-	-
Determine IP Dose and Schedule [e, d]	X	-	-	-	-	-	-
Physical Examination [f]	X	X	X	-	X	X	-
Vital Signs, Body Weight and Height [f]	X	X	X	-	X	X	-
Clinical Assessment [g]	X	X	X	-	X	X	-
Hematology [h]	X	X	X	X	X	X	-
Serum Chemistry [i]	X	X	X	X	X	X	-
Pregnancy Test [j, d]/Contraception Education [j]	X	X	X	X	X	X	-
Assessing Adverse Events [k, d]	X	X	X	-	X	X	-
Concomitant Medications/Procedures [d]	X	X	X	X	X	X	-
Dispense IP [l, d]	-	X	X	X	-	-	-
IP Diary Card	-	X	X	X	-	-	-
Collect Unused CC-486 [m]	-	-	X	-	X	-	-
Review IP Diary Card [m]	-	-	X	-	X	-	-
Subject Contact during Non-clinic Visits [b]	-	-	-	X	-	-	-
Survival Follow-up [n, d]	-	-	-		-	-	X

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRF = case report form; FCBP = females of child-bearing potential; IP = investigational product; RT-PCR = reverse transcription polymerase chain reaction.

[a] 7-day window for all visits, unless otherwise specified.

[b] When local, state and federal regulations allow for a site to ship IP to a subject's home, clinic visits are not necessary at every cycle, provided the following procedures are performed prior to dispensing (shipping) IP:

- *Hematology and serum chemistry assessments may be done locally and results sent to Investigator and/or site.*
- *Site personnel will telephone the subject to inquire about and record adverse events (AEs), concomitant medications/procedures and information from the IP diary – ie, any missed days/doses. Review of the IP diary for all cycles should be performed when subjects return to the clinic.*
- *The Investigator will review the laboratory test results, recorded as AEs, concomitant medication and IP dosing information.*
- *If the Investigator agrees, the subject may be dispensed another cycle of IP and arrangements will be made with the site pharmacy to ship IP to the subject's home. Additional IP diaries should be given to the subject during a clinic visit or shipped with the IP.*
- *Coordination of the timing of the laboratory tests, telephone call to the subject and shipment of the IP should be considered to avoid delays in starting the next cycle of treatment.*
- *If the subject communicates that he or she experienced an* AE *which the Investigator suspects may be serious, the subject will be instructed to return to the clinic for evaluation by the Investigator before continuing IP or receiving another cycle of IP. If the subject experienced a serious adverse event (SAE) the Investigator must report the event as described in Section 10.2.*
- *Subjects must have clinic visits at least once every 3 cycles.*

[c] Safety Follow-up visit occurs approximately 28 days after the last dose of IP.

[d] Data should be collected in the CRF.

[e] Subject's last dose and schedule in the parent CC-486 study will be starting dose and schedule in this study. Should be recorded in the CRF.

[f] Assessment if deemed necessary. This may include physical examination, vital signs, body weight – however, data will not be collected in the CRF but recorded in the source documents. Clinically significant abnormal findings should be recorded as AEs in the clinical database.

[g] Clinical assessment may be performed less frequently than every clinic visit, however, subjects must have clinical assessment at least every third cycle.

[h] Hematology: hemoglobin, hematocrit, red blood cell (RBC) count with indices (mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], and mean corpuscular hemoglobin concentration [MCHC]), white blood cell (WBC) count with absolute and percent differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils and myeloblasts [percent only]), platelet count. This information is required for safety monitoring only and laboratory test results will not be collected in the clinical database as described in Section 10.3.

[i] Serum chemistry of albumin, alkaline phosphatase, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), phosphorous, potassium, magnesium, serum glutamic oxaloacetic transaminase (SGOT [AST]), serum glutamic pyruvic transaminase (SGPT [ALT]), sodium, total and direct/indirect bilirubin, total protein, and uric acid. This information is required for safety monitoring only and laboratory test results will not be collected in the clinical database as described in Section 10.3

[j] For details on Contraception Education, please refer to Appendix C. For FCBP, a medically supervised serum pregnancy test is to be obtained and verified negative at screening. Note that the screening pregnancy test can be used as the test prior to starting study therapy in the treatment phase if it is performed within the 72-hour time frame. The subject may not receive IP until the investigator has verified that the result of the pregnancy test is negative. Serum pregnancy test during screening should be submitted to the local laboratory. Females under the age of 55 years must have a serum follicle-stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause. This will be collected locally at screening.

[k] Please refer to Section 6.1.7.

[l] Only one cycle of IP may be dispensed at one time. Subjects who received placebo in the parent CC-486 study will not receive IP.

[m] For subjects who do not visit clinic monthly, IP accountability and review of IP diary card is done during clinic visits.

[n] Overall survival measurements will include survival and disease status, and anticancer treatment not previously reported.

6. PROCEDURES

All of the required assessments are indicated in Table 4 with an "X" for the assessments to be performed during that visit. All data obtained from these assessments must be present in the subject's source documentation. Assessments and sample analysis will be performed locally and are described in detail below.

Additional assessments may be necessary in some subjects based on the parent CC-486 study protocol. These assessments may be performed at the discretion of the treating physician according to the local clinical practices and must be documented in the subject's source documentation.

6.1. Study Entry/Screening Assessment Phase

To ensure no or minimal gaps in IP dosing for subjects transitioning into the rollover protocol, study entry/screening assessment procedures should start immediately after discontinuation from the parent CC-486 study. Ideally, Day 1 of the first cycle in the rollover study should occur on the same day as the End of Study visit from the parent CC-486 study. Assessments performed as part of the End of Study visit from the parent CC-486 study do not need to be repeated on Day 1 of the rollover study if performed within 7 days (excluding the pregnancy testing for FCBP, which must be completed within 72 hours of Day 1 of each cycle).

Written informed consent must be obtained before any study-specific procedures are performed and any samples are collected. Study entry/screening assessments to confirm eligibility must take place within 21 days prior to enrollment. To ensure that inclusion and exclusion criteria are satisfied, eligibility for each subject will be reviewed by the sponsor prior to enrollment. Failure to meet any entry criterion excludes a subject from enrollment into the study.

Please refer to Section 6.1.9 for information to be collected on subjects who could not meet eligibility criteria.

Although PE, vital signs and clinical laboratory assessments are performed and must be present in the subject's source documentation, only concomitant medications/procedures and AEs are reported in the clinical CRF database.

6.1.1. Demographics

The subject number and protocol identifier from the parent CC-486 study, the subject number from this rollover study, date of birth, sex, race, and ethnicity will be recorded on the respective CRF(s) during Study Assessment/Screening Phase.

6.1.2. Clinical Assessments

Clinical assessment should be performed if deemed necessary by the Investigator for the clinical management of the subject. Assessment by the Investigator may be performed less frequently than at the beginning of each cycle, however, subjects must have clinical assessment as stipulated in Table 4 at least every third cycle; although pregnancy testing for FCBP must be performed, and verified as negative, prior to the subject starting every new cycle.

6.1.3. Physical Examination

Information about the PE must be present in the subject's source documentation. Although a PE is performed, it is not reported in the database.

Please refer to Table 4 for specific time points of this assessment.

6.1.4. Vital Signs, Body Weight, and Height Measurements

Vital signs include blood pressure, pulse, body temperature, body weight, and respiratory rate. Height is collected only during Study Entry/Screening Assessment Phase. Although vital signs, body weight, and height measurements are performed and recorded in the source documentation, they are not reported in the database.

Please refer to Table 4 for specific time points of these assessments.

6.1.5. Hematology

A complete blood count (CBC) for the hematology assessment includes:

- red blood cell (RBC) count
- hemoglobin
- hematocrit
- mean corpuscular volume (MCV)
- mean corpuscular hemoglobin (MCH)
- mean corpuscular hemoglobin concentration (MCHC)
- red cell distribution width (RDW)
- platelet count
- white blood cell (WBC) count with differential:
  - absolute and/or percent neutrophils
  - absolute and/or percent lymphocytes
  - absolute and/or percent monocytes
  - absolute and/or percent eosinophils
  - absolute and/or percent basophils
  - percent myeloblasts, if reported.

Hematology samples will be analyzed by the local laboratory. Any or all laboratory assessments may be repeated more frequently if clinically indicated. Please refer to Table 4 for specific time points of this assessment. Although hematology samples are collected, analyzed and recorded in the source documentation, they are not reported in the database.

6.1.6. Serum Chemistry

Serum chemistry assessments include:

- potassium
- sodium
- chloride

- bicarbonate
- calcium
- magnesium
- phosphorus
- blood urea nitrogen (BUN)
- creatinine
- glucose
- albumin
- total protein
- alkaline phosphatase
- lactate deyhydrogenase (LDH)
- uric acid
- total and direct/indirect bilirubin
- aspartate aminotransferase (AST) or serum glutamic oxaloacetic transaminase (SGOT)
- alanine aminotransferase (ALT) or serum glutamic pyruvic transaminase (SGPT)

Serum chemistry samples will be analyzed by the local laboratory. Any or all laboratory assessments may be repeated more frequently if clinically indicated. Please refer to Table 4 for specific time points of this assessment. Although serum chemistry samples are collected, analyzed and recorded in the source documentation, they are not reported in the database.

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6.1.7. Assessing Adverse Events

Adverse events will be collected beginning on the date the informed consent is signed. Adverse events will be recorded on the respective CRF(s). All subjects will be monitored for AEs during the study as outlined in Section 10. Please refer to Section 10 for details regarding monitoring, recording, and reporting of AEs, including serious adverse events (SAEs).

For subjects entering the CC-486-GEN-001 rollover study, ongoing AEs at the time of the End of Study visit from the parent CC-486 study should be left as ongoing and should not be recorded again in the rollover protocol AE CRF unless there is a worsening in the intensity of the ongoing AE. Adverse events with an onset date between the End of Study visit from the parent CC-486 study and up to the time of signing the informed consent of the rollover study should be recorded in the AE CRF for the parent CC-486 study, if the AE occurred within 28 days after the last dose of IP in the parent CC-486 study. Only new AEs with an onset date on or after the signing of the informed consent in the rollover study should be recorded in the rollover study AE CRF. If a previously reported AE during the parent CC-486 study worsens during the rollover study, then the AE should be recorded as a new AE with a higher grade on the rollover AE CRF. All subjects will be monitored for AEs from the signing of the informed consent through 28 days following the date of last dose of CC-486 in the rollover protocol.

6.1.8. Concomitant Medications/Significant Non-drug Therapies/Concomitant Procedures

All prescription or over-the-counter medications and therapeutic procedures administered during Study Entry/Screening Assessment Phase and until 28 days after the last dose of the IP must be recorded on the respective CRF. Please refer to Table 4 for specific time points of this assessment.

6.1.9. Information to be Collected on Subjects Who do not Meet Eligibility Criteria (Not Applicable to Subjects Who Enter Follow-up Phase of the Study)

The following must be collected for all subjects who provide informed consent, but fail eligibility criteria and are not enrolled in the treatment phase of the study:

- informed consent date;
- reason subject did not qualify for the study;
- Investigator's signature.

Any adverse events experienced by subjects who do not meet eligibility criteria will be collected from the date of signing informed consent to the day the subject is declared a screen failure. This information is to be captured in the subject's source documents and appropriate CRF(s). Relevant information will also be recorded on a study entry/screening assessment log.

6.2. Treatment Phase

Once eligibility is confirmed, the investigative site should contact Integrated Response Technology (IRT) and the IP (CC-486) to subjects will be assigned via IRT. The dose and schedule of CC-486 in this study will be dictated by which parent CC-486 study the subject participated in, taking into account their last dose and schedule of CC-486 in the parent CC-486 study. For some subjects, a formulation change of the IP from capsule formulation to tablet formulation may occur after enrolling into this rollover study.

Subjects who received placebo in the parent CC-486 clinical trials may transition into the rollover protocol, however, they will not receive CC-486 treatment. Once consented these subjects will directly enter the follow-up phase of the rollover study and will be followed for survival.

6.2.1. Cycle 1 Procedures/Assessments

Cycle 1 Day 1 predose assessments may be waived, if subjects had their End of Study assessments and/or study entry/screening assessments performed within 7 days of Cycle 1 Day 1. The pregnancy test can be waived for FCBP only if it was performed within 72 hours prior to IP administration.

- Clinical assessment by Investigator
- Hematology
- Serum chemistry
- Pregnancy test for FCBP/contraception education
- Collect concomitant medications/procedures
- AE assessment

- IP dispensing (for 28-day cycle)
- Provide IP diary card

Clinical assessment by the Investigator will be performed at clinic visits. This may include PE, vital signs, and body weight but data will not be collected in the CRF. Clinically significant abnormal findings on these assessments should be recorded as AEs in the clinical database. Unscheduled visits may be performed if deemed necessary by the Investigator.

6.2.1.1. Cycle 2 and Beyond Procedures/Assessments (if Subject is Visiting the Clinic)

- Clinical assessment by Investigator
- Hematology
- Serum chemistry
- Pregnancy test for FCBP/contraception education
- Collect concomitant medications/procedures
- AE assessment
- Review IP diary card from prior cycle(s) which includes antiemetic premedication use
- Drug accountability – collect unused oral azacitidine
- IP dispensing (for 28-day cycle)
- Provide IP diary card

Clinical assessment by the Investigator will be performed at clinic visits. This may include PE, vital signs, and body weight but data will not be collected in the CRF. Clinically significant abnormal findings on these assessments should be recorded as AEs in the clinical database.

6.2.1.2. Cycle 2 and Beyond Procedures/Assessments (if Subject is Not Visiting the Clinic)

When local, state and federal regulations allow for a site to ship IP to a subject's home, clinic visits are not necessary at every cycle, provided the following procedures are done prior to dispensing (shipping) one cycle of IP (this does not include FCBP, who must visit the clinic before each cycle for pregnancy testing):

- Hematology and serum chemistry may be done locally with results sent to the Investigator and/or site.
- Site personnel will telephone the subject to inquire about and record AEs, concomitant medications/procedures and information from the IP diary – ie, any missed days/doses. Review of the IP diary for all cycles should be performed when the subject returns to the clinic.
- The Investigator will review the laboratory test results, recorded AEs, concomitant medication and IP dosing information.
- If the Investigator agrees, the subject may be dispensed another cycle of IP and arrangements will be made with the site pharmacy to ship IP to the subject's home. Additional IP diaries should be given to the subject during a clinic visit or shipped with the IP.

- Coordination of the timing of the laboratory tests, telephone call to the subject and shipment of the IP should be considered to avoid delays in starting the next cycle of treatment.
- If the subject communicates that he or she experienced an AE which the Investigator determines to be serious, the subject will be instructed to return to the clinic for evaluation by the Investigator before continuing IP or receiving another cycle of IP. If the subject experienced an SAE the investigator must report the event per Section 10.2 of the protocol.

Subjects must have clinic visits at least once every 3 cycles, except for a subject who is an FCBP. Any subject who is an FCBP must visit the clinic at the beginning of each cycle.

The study events schedule is described in Table 4.

6.2.2. End of Treatment

End of Treatment evaluation will be performed for subjects who are withdrawn from treatment for any reason as soon as possible after the decision to permanently discontinue treatment has been made.

The following evaluations will be performed as specified in the Table of Events (Table 4):

- Clinical assessment by Investigator
- Hematology
- Serum chemistry
- Pregnancy test for FCBP/contraception education
- Collect concomitant medications/procedures
- Adverse events assessments
- Collect any unused CC-486 and perform drug accountability (discontinuation from treatment visit)
- Review IP diary card from prior cycle(s) which includes antiemetic premedication use (discontinuation from treatment visit)

Clinical assessment by the Investigator will be performed at clinic visits. This may include PE, vital signs, and body weight but data will not be collected in the CRF. Clinically significant abnormal findings on these assessments should be recorded as AEs in the clinical database.

6.3. Follow-up Phase (Disregard if Not Applicable)

6.3.1. Safety Follow-up

All subjects will be followed for 28 days after the last dose of IP for AE reporting, as well as SAEs made known to the Investigator at any time thereafter that are suspected of being related to IP, as described in Section 10.1.

The following evaluations will be performed as specified in the Table of Events (Table 4):

- Clinical assessment by Investigator
- Hematology

- Serum chemistry
- Pregnancy test for FCBP/contraception education
- Collect concomitant medications/procedures
- Adverse events assessments

Clinical assessment by the Investigator will be performed at clinic visits. This may include PE, vital signs, and body weight but data will not be collected in the CRF. Clinically significant abnormal findings on these assessments should be recorded as AEs in the clinical database.

6.3.2. Survival Follow-up or Long-term Follow-up

Only those subjects whose parent CC-486 study required follow-up for survival will be followed for overall survival. During the follow-up phase of the study, subjects will be followed for survival every month for the first year and then every 3 months until death, withdrawal of consent for further follow-up, study termination, until a subject is lost to follow-up, according to the parent CC-486 protocol requirements.

New anticancer therapies should be collected at the same time schedule.

Survival/long-term follow-up may be conducted by record review (including public records) and/or telephone contact with the subject, family, or the subject's treating physician.

7. DESCRIPTION OF STUDY TREATMENTS

7.1. Description of Investigational Product(s)

The Sponsor will supply CC-486 100-, 150-, 200-, and 300-mg tablets for oral administration. Each tablet is formulated using excipients that are generally regarded as safe and are used in marketed drug products.

All tablets will be packaged in blister cards. Only sufficient IP for one cycle of treatment will be provided to each subject at the start of each treatment cycle. All tablets should be swallowed whole, and should not be broken or chewed.

IP will be shipped, and subjects instructed to store IP, at ambient temperatures as directed on the package label. Shelf-life evaluation of the intact blister card is ongoing. The IP will be monitored for stability for the duration of the study.

7.2. Treatment Administration and Schedule

7.2.1. Investigational Product Treatment Schedule

The dose and schedule of CC-486 in this study will be dictated by which parent CC-486 study the subject participated in. The subjects will continue at the same dose, schedule or frequency used for the last dose of CC-486 given in the parent CC-486 study. For some subjects, a formulation change of the IP from capsule formulation to tablet formulation will occur after enrolling into this rollover study. Antiemetics are not required during the study; however, at the Investigator's discretion, subjects may receive prophylactic antiemetics approximately 30 minutes prior to each dose of CC-486, or as administered in the parent CC-486 study. Subjects may continue to receive

the protocol-prescribed therapy for as long as they benefit from the treatment or until treatment is discontinued for reasons detailed in Section 11. The decision to discontinue a subject remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, prior to discontinuing a subject, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

7.2.2. Investigational Product Dispensation

Investigational product will be dispensed on Day 1 of each treatment cycle. Only 1 cycle of IP will be dispensed to the subject on Day 1 of each treatment cycle.

The subject may not receive IP for each treatment cycle until all Day 1 procedures have been completed and all IP from the previous cycle are to be accounted for (where applicable). During subject's non clinic visit cycles, IP accountability information (any missed days/doses) will be collected over telephone by the site personnel, and verified during the subject's next clinic visit (subjects will be instructed to record all dosing information in the subject's IP dairy on an ongoing basis).

When local, state and federal regulations allow for a site to ship IP to a subject's home, only one cycle of IP may be shipped each time.

Female subjects of childbearing potential must visit the clinic every cycle. For FCBP subjects, a pregnancy test must be performed and verified as negative within 72 hours prior to IP administration on Day 1 of each new cycle.

7.2.3. Investigational Product Administration

Investigational product administration will be accurately recorded including, but not limited to, date of administration, dose, and any changes in dose administration (eg, interruption or reduction in dose due to an AE).

The initial dose of CC-486 in the CC-486-GEN-001 protocol is to be taken at the same dose, schedule and frequency used for the last dose of CC-486 given in the parent CC-486 study. Investigational product will be administered by the study site personnel in the clinic on Day 1 of Cycle 1. The subject will self-administer all other IP doses in the treatment phase.

Antiemetic medication (not a required study medication) may be taken 30 minutes prior to IP administration. Subject should ingest IP with approximately 240 mL (8 ounces) of room temperature water. Oral azacitidine tablets should not be split or crushed. Investigational product can be taken on an empty stomach or with food. If following CC-486 administration an emesis event occurs, subjects should not take additional IP on that same day, but return to the normal time of dose administration the following day. It is recommended that the subject receives an antiemetic 30 minutes prior to each CC-486 dose for the first 2 treatment cycles. Antiemetic prophylaxis may be omitted after 2 cycles if there is no nausea or vomiting.

7.2.4. Missing Doses

All efforts should be made to administer IP on all of the scheduled days of each of the scheduled days of the treatment cycle. A dose should be administered at about the same time each day. If a

dose of CC-486 is missed or is not taken at the usual time, the dose should be administered as soon as possible on the same day and returned to the normal time of dose administration on the following day. Two doses should not be taken on the same day. Any missed doses during that cycle should not be taken after the last scheduled day of administration for the cycle, but instead should be returned by the subject for IP accountability.

7.2.5. Overdose

Overdose, as defined for this protocol, refers to CC-486 dosing only.

On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of CC-486 assigned to a given subject, regardless of any associated AEs or sequelae:

- Oral - any amount over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the CRF. See Section 10.1 for the reporting of AEs associated with overdose.

7.2.6. Dose Modifications

Subjects should be monitored for toxicity using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, as a guide for the grading of severity.

At the discretion of the Investigator, all dose modifications due to toxicity in individual subjects may be performed as described in the parent CC-486 study protocol or can follow the steps provided below in this protocol (Table 5:.

Dose modification is only available at the beginning of each cycle (ie, intra-cycle dose modification is not allowed).

Dose Adjustment Guidelines For Subjects Who Are on QD Schedule

All subjects who experience significant toxicity possibly or probably related to oral azacitidine should have the dose of oral azacitidine reduced in 100 mg increments to a minimum dose of 100 mg/day, irrespective of the starting dose, in a stepwise fashion as follows

- from 500 mg/day to 400 mg/day
- from 400 mg/day to 300 mg/day
- from 300 mg/day to 200 mg/day
- from 200 mg/day to 100 mg/day

Dose Adjustment Guidelines for Subjects Who Are on BID Schedule

All subjects who are on a twice a day (BID) schedule and who experience significant toxicity possibly or probably related to oral azacitidine should have the dose of oral azacitidine reduced to a minimum dose of 100 mg BID, irrespective of the starting dose, in a stepwise fashion as follows:

- from 300 mg BID to 200 mg BID
- from 200 mg BID to 100 mg BID

Dose Schedule Modification

If toxicity persists even after a step-wise dose reduction to a minimum of 100 mg QD or 100 mg BID, a maximum of two treatment schedule modifications is permitted for subjects who are on a 21-day schedule

- from 21 to 14 days,
- then 14 days to 7 days

and a single treatment schedule modification for subjects who are on a 14-day schedule

- from 14 to 7 days

is permitted in the event of continuing toxicity that does not respond to dose reduction.

For subjects who are already on a 7-day dosing schedule no further reduction in the dosing schedule of 100 mg daily is permitted.

If toxicities persist or recur even after the dose is reduced to a minimum dose of 100 mg and the dose schedule is reduced to 7 days, oral azacitidine should be discontinued. The Sponsor's Medical Monitor must be consulted prior to any dose reduction step or treatment termination.

The decision to modify a dose or a subject's treatment schedule should first be discussed with the Medical Monitor or designee. Subjects should not receive less than 100 mg IP or be scheduled to receive treatment for less than 7 days.

Table 5: Criteria for Interrupting or Resuming Study Treatment

Toxicity (NCI CTCAE Toxicity Grade)	Resolution
Grade 4 neutropenia or Febrile Neutropenia ≥ Grade 3	First Occurrence: • Interrupt dose. Resume the treatment cycle at the same dose once neutrophils return to Grade 2 or lower. • The use of supportive care such as G-CSF, as clinically indicated, may be considered. Occurrence in 2 Consecutive Cycles: • Interrupt dose. After neutrophils return to Grade 2 or lower, resume the treatment cycle at a reduced dose as indicated in Section 7.2.6. • If a subject continues to experience the toxicity after dose reduction, reduce the treatment duration by 7 days. • If the toxicity continues or re-occurs after dose and schedule reduction, discontinue oral azacitidine. • The use of supportive care such as G-CSF, as clinically indicated, may be considered.

Table 5: Criteria for Interrupting or Resuming Study Treatment

Toxicity (NCI CTCAE Toxicity Grade)	Resolution
Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding	First Occurrence: • Interrupt dose. Resume the treatment cycle at the same dose once platelets return to Grade 2 or lower. Occurrence in 2 Consecutive Cycles: • Interrupt dose. After platelets return to Grade 2 or lower, resume the treatment cycle at a reduced dose as indicated in Section 7.2.6. • If a subject continues to experience the toxicity after dose reduction, reduce the treatment duration by 7 days. • If the toxicity continues or reoccurs after dose and schedule reduction, discontinue oral azacitidine.
Diarrhea, nausea or vomiting ≥ Grade 3	• Interrupt dose. Resume the treatment cycle at the same dose once toxicity has resolved to Grade 1 or lower. • Use supportive care such as anti-emetic therapy and treat diarrhea at the onset of symptoms. • If event reoccurs, interrupt dose until resolved to Grade 1 or lower. Reduce the dose as indicated in Section 7.2.6. • If a subject continues to experience the toxicity after dose reduction, reduce the treatment duration by 7 days. • If the toxicity continues or re-occurs after dose and schedule reduction, discontinue oral azacitidine. • Follow recommendations in Appendix B for treatment-induced diarrhea.
Other non-hematological AEs ≥ Grade 3	• Interrupt dose and provide medical support according to local recommendation. Resume treatment cycle at same dose once toxicity has resolved to Grade 1 or lower. • If the event reoccurs, interrupt dose until resolved to Grade 1 or lower and reduce dose as indicated in Section 7.2.6. • If a subject continues to experience the toxicity after dose reduction, reduce the treatment duration by 7 days. • If the toxicity continues or reoccurs after dose and schedule reduction, discontinue oral azacitidine.
Weight Change: No treatment adjustment for weight loss or gain alone**.** The reason for weight loss (eg, nausea, vomiting, anorexia) or weight gain (eg, peripheral edema) may require a treatment modification. Note: Advised to follow specific criteria from the parent CC-486 protocol.	

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; G-CSF = granulocyte colony-stimulating factor; IP = investigational product; NCI = National Cancer Institute.

7.2.7. Re-treatment Criteria

At the discretion of the Investigator, re-treatment criteria in individual subjects may be performed as described in the parent CC-486 study protocol or can follow the steps provided below in this protocol.

In order to proceed to the next cycle, subjects must continue to meet entry criteria regarding renal and hepatic function (see Section 7.3). Therefore, subjects will have laboratory assessments performed to evaluate organ function prior to starting each cycle (including Cycle 1). Because of the time it takes to obtain results from the central laboratory, samples should be collected early enough prior to the start of the next cycle in order to allow sufficient time for review.

The start of the next cycle will be delayed if the subject does not meet entry criteria regarding renal and hepatic function. If there is a delay of more than 42 days (6 weeks) in the start of the next cycle, the Medical Monitor must be consulted. Study treatment should be discontinued if there is a delay of more than 56 days (8 weeks) in the start of the next cycle, unless, in the opinion of the Investigator and the Medical Monitor, the subject is experiencing clinical benefit. Justification for the subject continuing in the study must be recorded in the source documents.

The decision to discontinue a subject from IP, which will not be delayed or refused by the Sponsor, remains the responsibility of the treating physician. However, prior to discontinuing a subject, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

7.3. Method of Treatment Assignment

Subjects who enter the Study Assessment/Screening Phase will be assigned a new, site specific subject number. All eligible subjects who enter treatment phase will receive CC-486.

All IP will be managed by the IRT system as a central subject number assignment and accountability tool only.

7.4. Packaging and Labeling

The label(s) for IP will include Sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

7.5. Investigational Product Accountability and Disposal

Investigational product accountability will be assessed by the Investigator or designee. Applicable information such as lot number, tablet count and expiration date should be collected, as well as information provided by the subject or the caregiver (eg, subject IP dosing diary).

Investigational product accountability should be assessed before IP dispensing for each subsequent treatment cycle in the treatment phase, starting on Day 1 of Cycle 2, and at the End of Treatment visit. During subject's non clinic visit cycles, IP accountability information (any missed days/doses) will be collected over telephone by the site personnel, and verified during the subject's

next clinic visit (subjects will be instructed to record all dosing information in the subject's IP dairy on an ongoing basis).

The Investigator(s) or designee(s) is responsible for accounting for all IP that is issued to and returned by the subject during the course of the study according to applicable regulatory requirements. Any unused IP must be returned by a study subject and retained by the investigative site for accountability to be conducted by a Sponsor representative (or designee). If any IP is lost or damaged, its disposition should be documented. At the periodic monitoring visits, a Sponsor representative (or designee) will conduct IP accountability and address any discrepancies. Upon satisfactory reconciliation of all IP, returned IP may be destroyed. At the conclusion of the study, all remaining IP will be counted, reconciled with dispensing records, documented, and destroyed at the clinic site or allocated drug destruction location after completion of drug accountability by a Sponsor representative (or designee). The Sponsor representative (or designee) will ensure that a final report of drug accountability to the unit dose level (ie, tablet) is prepared and placed in both the Investigator study file and the central clinical study file.

The Sponsor (or designee) will instruct the Investigator(s) on the return, disposal and destruction of IP. A copy of the site's standard operating procedure (SOP) for IP destruction may be collected by the Sponsor (or designee). Any revisions to a site's destruction process must be provided and approved by the Sponsor (or designee) prior to implementation on this protocol. Any site without a Sponsor (or designee) approved destruction SOP and process will be required to return IP to Celgene.

The Sponsor representative (or designee) will review with the Investigator and relevant site personnel the process for IP return, disposal, and/or destruction including responsibilities for the site versus the Sponsor (or designee).

7.6. Investigational Product Compliance

Investigational product will be administered by the study site personnel in the clinic on Day 1 of Cycle 1. Subjects will self-administer all other IP doses in the treatment phase. Documentation of dosing during treatment will be recorded in a study specific diary card. Investigational product administration diary cards will be provided by the Sponsor to study site personnel, who will in turn distribute them to study subjects. Study site personnel will enter the scheduled daily doses, the number of tablets to be taken each day and any other applicable information. Study site personnel will review the dosing information with the subject (or legally authorized representative) on scheduled clinic visit days. Subjects (or legally authorized representative) will be asked to record IP dosing information and antiemetic medication taken at home in the diary card and to bring the diary card and unused tablets in the blister card (or the blister card packaging even if it is empty) with them to scheduled clinic visits (ie, prior to the start of the next treatment cycle). A diary card and tablet compliance check will be performed by study personnel. Diary cards must be saved and kept with the source documentation. Study site personnel will perform an IP administration compliance check and record this information in the subject's source documentation.

During subject's non clinic visit cycles, IP accountability information (any missed days/doses) will be collected over telephone by the site personnel, and verified during the subject's next clinic visit

(subjects will be instructed to record all dosing information in the subject's IP dairy on an ongoing basis).

Administration of all IP will be recorded including dispensing, dosing and any changes in dosage administration such as interruption or reduction in dosing due to an AE.

8. CONCOMITANT MEDICATIONS AND PROCEDURES

All prior and concomitant medications (prescription and non-prescription) and/or procedures that are administered during the Study Entry/Screening Assessment Phase prior to the start of IP through to the last dose of IP, or up to the End of Treatment visit, whichever period is longer, must be recorded on the appropriate CRF. Significant non-drug therapies and concomitant procedures administered following the first dose of IP through to the last dose of IP, or up to the End of Treatment visit, whichever period is longer, must be recorded on the appropriate CRF.

Prior treatment with ESAs, thrombopoiesis-stimulating agent, iron-chelation therapy and other medications considered supportive care should be recorded regardless of the discontinuation date of treatment.

Concomitant medications/procedures, if considered necessary for the subject's welfare and are unlikely to interfere with the IP, may be given at the discretion of the Investigator.

8.1. Permitted Concomitant Medications and Procedures

Best supportive care may be used in combination with study treatment as deemed necessary. Best supportive care will include, but not be limited to, RBC and platelet transfusions, use of an ESA, antibiotic, antiviral, and antifungal therapy, nutritional support, and G-CSFs for subjects experiencing neutropenic infections, thus the risk of not providing subjects with appropriate care is minimized. The use of these products will be considered as concomitant treatment and documented as concomitant medications, therapies or procedures.

The use of myeloid growth factors (G-CSF) and granulocyte macrophage colony-stimulating factor [GM-CSF]) may be permitted per the Investigator's discretion and according to American Society of Clinical Oncology and European Society for Medical Oncology guidelines only for the treatment of neutropenic infections. For subjects who develop an absolute neutrophil count (ANC) $< 0.5 \times 10^9$/L, administration of prophylactic fluoroquinolone antibiotics (eg, ciprofloxacin or levofloxacin) or other prophylactic antibiotic treatments used as standard treatment at the site is allowed and must be documented as a concomitant medication on the appropriate CRF. If neutropenic infection occurs, treatment should consist of a broad spectrum antibiotic, and if the Investigator deems the use of a myeloid growth factor to be medically important, G-CSF may also be administered. If myeloid growth factors are administered, they should be stopped within 4 days following resolution of the febrile episode. In addition, the subject's response to protocol-defined treatment should not be assessed until at least 3 weeks following the last dose of G-CSF to avoid confusing relapse of disease, when it may have been related to growth factor.

A serotonin ($5\text{-}HT_3$) receptor antagonist (eg, ondansetron, or other comparable medication) may be administered as an antiemetic approximately 30 minutes prior to administration of IP.

Pretreatment or posttreatment with a serotonin (5-HT_3) receptor antagonist (or other antiemetic medication) will be considered as concomitant therapy and should be recorded on the appropriate CRF.

Treatment with antidiarrheal medications should be prescribed at the first sign of diarrhea. Premedication with antidiarrheal medication for subsequent doses of CC-486 may be appropriate at the Investigator's discretion (Appendix B).

Parenteral flu vaccination is permitted.

Coronavirus disease 2019 (COVID-19) vaccines that are NOT live can be administered during the study, including during CC-486 treatment and after the last administration of CC-486. COVID-19 vaccines that are NOT live should be handled in the same manner as other vaccines. The following are NOT considered live vaccines and the decision to vaccinate should be made by the investigator and subject: inactivated vaccines (eg, heat-killed and formalin-killed vaccines), subunit vaccines, toxoid vaccines, nucleic acid vaccines that do not encode potentially infectious virus (eg, Pfizer/BioNTech and Moderna COVID-19 vaccines), and replication-incompetent recombinant vector vaccines.

No data are available on the response to COVID-19 vaccines. Non-live COVID-19 vaccination is considered a simple concomitant medication within the study. However, the efficacy and safety of non-live vaccines (including non-live COVID-19 vaccines) in subjects receiving CC-486 in this trial is unknown. Please contact the Medical Monitor with any questions related to COVID-19 vaccines.

8.2. Prohibited Concomitant Medications and Procedures

Other investigational therapies must not be used while the subject is enrolled in the study.

Anticancer therapy (chemotherapy, biologic or investigational therapy, immunotherapy, anticancer hormonal therapy, radiotherapy and surgery) other than the study treatments must not be given to subjects during the study. If such treatment is required, the subject must be discontinued from the study.

The administration of either α-interferon and/or ribavirin, or drugs with known renal toxicity is prohibited during study treatment.

Drug-drug interactions have not been investigated with CC-486 in clinical studies. CC-486 does not inhibit or induce major cytochrome P450 (CYP) enzymes and is not an inhibitor of major uptake and efflux drug transporters at clinically relevant concentrations; thus, oral azacitidine has minimal potential to cause drug-drug interactions with co-administered CYP or transporter substrates.

Live COVID-19 vaccines should generally not be administered to a participant during the study, including during the treatment period, safety follow-up period, and within 3 months following last dose of IP. Live vaccines are defined as those that are capable of transmitting infectious severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or other viruses. If it cannot be

determined whether or not the vaccine is live, it is recommended that the vaccine not be administered until it is confirmed that there is no risk of viral infectivity within the participant.

No data are available on the response to COVID-19 vaccines. The efficacy and safety of vaccination in subjects who are receiving CC-486 are unknown. Please contact the Medical Monitor with any questions related to COVID-19 vaccines.

Oral azacitidine should not be used interchangeably with injectable azacitidine due to differences in exposure, and the dose and schedule recommendations. Verify drug name, dose, and administration route.

8.3. Required Concomitant Medications and Procedures

Not applicable.

9. STATISTICAL CONSIDERATIONS

The sections below provide an overview of the proposed statistical considerations and analyses.

9.1. Overview

The objective of the statistical analysis is to evaluate the long-term safety of single agent CC-486 in subjects who received single agent CC-486 in other Celgene sponsored CC-486 trials.

All data will be summarized by treatment regimen. Summaries of continuous variables will present the number of subjects included in the analysis (N), the mean and standard deviation (SDev) of the mean, the median, the minimum, and the maximum statistics. Counts and percentages will be presented in summaries of categorical variables. The denominator for each percentage will be the number of subjects in the population treatment regimen unless otherwise specified. In general, missing data will not be imputed unless otherwise specified.

9.2. Study Population Definitions

9.2.1. Enrolled Population

The Enrolled population includes all subjects who sign an informed consent.

9.2.2. Safety Population

The Safety population includes all enrolled subjects who were determined eligible to receive IP in the study. The Safety population will be used for all safety analyses. Subjects will be analyzed according to the treatment regimen actually received.

9.3. Sample Size and Power Considerations

The size of this study will be defined by the number of subjects rolling over to this study from parent CC-486 studies.

9.4. Background and Demographic Characteristics

Subjects' age and other continuous baseline characteristics will be summarized using descriptive statistics (N, mean, SDev, median, minimum, maximum), while gender, race and other categorical variables will be provided using frequency tabulations (count, percent) by treatment group.

9.5. Subject Disposition

Subject disposition (analysis population allocation, entered, screen failures, primary reason for screen failure, discontinued and primary reason for discontinuation, etc) will be summarized using frequency and percent for both treatment and follow-up phases. Protocol deviations will be summarized using frequency tabulations.

9.6. Overall Survival

OS analysis will be performed if it is required by the parent CC-486 protocol, and if the sample size and number of deaths allow to conduct the appropriate analysis. Deaths will also be summarized in safety tables or listings.

Overall survival (OS), defined as the time from randomization to death from any cause, will be calculated using the randomization date from the parent CC-486 study and date of death, or date of last follow-up for censored subjects as appropriately defined in the parent study. Time to death from any cause is defined as the time between randomization and death from any cause. Subjects will be followed until dropout, death, or study closure. Drop-out may be due to withdrawal of consent from further data collection or lost to follow-up. Subjects who drop out or are alive at study closure will have their OS times censored at the time of last contact, as appropriate.

The analysis of OS may be performed separately for each applicable parent CC-486 study. Overall survival curves will be estimated using Kaplan-Meier methods.

9.7. Safety Analysis

The analysis will be conducted in the safety population. Adverse events, death, concomitant medications/procedures and subsequent anticancer therapies will be tabulated and summarized across the study, by treatment regimen.

Adverse events observed will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. The severity of the toxicities will be graded according to the NCI CTCAE (Version 4.0) whenever possible. The frequency of AEs will be tabulated by MedDRA system organ class and preferred term. Subjects having the same event more than once will be counted only once in frequency tabulations. Treatment-emergent AEs (TEAEs) will be summarized by worst severity grade, system organ class, and preferred term. TEAEs leading to death or to discontinuation from treatment, TEAEs classified as CTCAE Grade 3 or Grade 4, TEAEs related to IP and treatment-emergent SAEs will be summarized separately. By-subject listings of all AEs, deaths and SAEs, regardless of when they occur, will be provided.

9.8. Interim Analysis

There is no interim analysis planned in this study.

9.9. Other Topics

Not applicable.

10. ADVERSE EVENTS

10.1. Monitoring, Recording and Reporting of Adverse Events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 10.3), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the CRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to an IP should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose CRF. (See Section 7.2.5 for the definition of overdose.) Any sequelae of an accidental or intentional overdose of an IP should be reported as an AE on the AE CRF. If the sequela of an overdose meets SAE criteria, then it must be marked as an SAE on the electronic case report form (eCRF). The overdose itself should not be reported as an AE.

In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for CC-486 overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological, or surgical findings, PE findings, or findings from other tests and/or procedures.

Adverse events of special interest (AESI) will be collected when applicable and if it is required in the parent CC-486 study protocol, and may include secondary primary malignancies, progression to AML for subjects with MDS, and other AESI specified in the parent CC-486 study.

All AEs will be recorded by the Investigator from the time the subject signs informed consent until 28 days after the last dose of IP as well as those SAEs made known to the Investigator at any time thereafter that are suspected of being related to IP. Adverse events and SAEs will be recorded on the AE page of the CRF and in the subject's source documents. Refer to Section 10.5 for instructions on how to report SAEs to Drug Safety. All SAEs must be reported to the Sponsor's Drug Safety within 24 hours of the Investigator's knowledge of the event.

The SAE is recorded within the eCRF and the data is transmitted electronically to the Sponsor's Drug Safety within 24 hours of the Investigator's knowledge of the event. In the event that electronic transmission is not available, a paper SAE Report Form will be completed and sent directly to the Sponsor's Drug Safety, ensuring the event is recorded on the eCRF as well.

Progressive disease will not be considered as an AE for subjects with AML. However, any sign, symptom, or manifestation of progressive disease will be considered as an AE (if they meet any of the seriousness criteria, they will considered as an SAE). Progression to AML will be considered as an AE for subjects with MDS and be reported as an AE in the eCRF.

In order to facilitate enhanced reporting of COVID-19 events that occur during the study, all AEs and SAEs after the time of consent that are related to SARS-CoV-2 or COVID-19 infection must be reported.

10.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

10.2.1. Seriousness

An SAE is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (ie, in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life-threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events **not considered** to be SAEs are hospitalizations for:

- a standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- the administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- a procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.

- hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- a procedure that is planned (ie, planned prior to start of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- an elective treatment of or an elective procedure for a pre-existing condition, unrelated to the studied indication, that has not worsened from baseline.
- emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to the IP, action taken regarding the IP, and outcome.

10.2.2. Severity/Intensity

For both AEs and SAEs, the Investigator must assess the severity/ intensity of the event.

The severity/intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of the Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0);
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40.

AEs that are not defined in the CTCAE should be evaluated for severity/intensity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
- Grade 4 = Life-threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death - the event results in death

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

10.2.3. Causality

The Investigator must determine the relationship between the administration of the IP and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected:	a causal relationship of the adverse event to IP administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	there is a **reasonable possibility** that the administration of IP caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP and the adverse event.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional IP that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

10.2.4. Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

10.2.5. Action Taken

The Investigator will report the action taken with IP as a result of an AE or SAE, as applicable (eg, discontinuation, interruption, or dose reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

10.2.6. Outcome

The Investigator will report the outcome of the event for both AEs and SAEs.

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered (returned to baseline), recovered with sequelae, or death (due to the SAE).

10.3. Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance, eg, one that indicates a new disease process and/or organ toxicity, or is an exacerbation or worsening of an existing condition.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

10.4. Pregnancy

All pregnancies or suspected pregnancies occurring in either a female subject of childbearing potential or partner of childbearing potential of a male subject are immediately reportable events.

10.4.1. Females of Childbearing Potential

Pregnancies and suspected pregnancies (including elevated βhCG or positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring while the subject is on IP, or within 6 months or longer if required by local regulations, of the subject's last dose of IP, are considered immediately reportable events. Investigational product is to be discontinued immediately and the subject instructed to return any unused portion of the IP to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by email, phone or facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

If the outcome of the pregnancy was abnormal (eg, spontaneous abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Sponsor's Drug Safety, within 24 hours of the Investigator's knowledge of the event.

10.4.2. Male Subjects

If a female partner of a male subject taking IP becomes pregnant while the subject is receiving investigational product, within 3 months, or longer if required by local regulations, of the last dose of IP, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately. The female partner should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for

further evaluation and counseling. Male subjects should avoid fathering a child until 3 months after the last dose of IP, or longer if required by local regulation. The Informed Consent Form (ICF) will address any country specific requirements as needed.

10.5. Reporting of Serious Adverse Events

Any AE that meets any serious criterion requires reporting as an SAE within 24 hours of the Investigator's knowledge of the event. This instruction pertains to initial SAE reports as well as any follow-up reports.

This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent until 28 days after the last dose of IP) or any SAEs made known to the Investigator at anytime thereafter that are suspected of being related to IP. Serious adverse events occurring prior to treatment (after signing the ICF) are to be recorded within the eCRF, but do not require reporting to the Sponsor's Drug Safety.

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board (IRB)/Ethics Committee (EC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

The SAE is recorded within the eCRF, and the data is transmitted electronically to the Sponsor's Drug Safety. In the event electronic transmission is not available, a paper SAE Report Form will be completed and sent directly to the Sponsor's Drug Safety, ensuring the event is recorded on the eCRF as well.

10.5.1. Safety Queries

Queries pertaining to SAEs will be communicated from the Sponsor's Drug Safety to the site via CRF (if electronic transmission is available), facsimile or electronic mail. The response time is expected to be no more than five (5) business days. Urgent queries (eg, missing causality assessment) may be handled by phone

10.6. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to CC-486 based on the Investigator Brochure.

In the United States, expedited reports sent to the Food and Drug Administration (FDA) by the Sponsor based on the reasonable possibility threshold are known as "Investigational New Drug safety reports" and will be reported in accordance with 21 CFR 312.32.

For reporting to the FDA, events that are not suspected to be related to CC-486 by the Sponsor will not be considered adverse reactions. As per FDA regulations, events that are anticipated in the study population listed in Section 10.2, will not be considered adverse reactions on individual assessment and will be reviewed on an aggregate basis for assessment of frequency.

For countries within the European Economic Area (EEA), the Sponsor or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, suspected unexpected serious adverse reactions (SUSARs) in accordance with

Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

The Sponsor or its authorized representative shall notify the Investigator of the following information:

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (ie, SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information on file including correspondence with Celgene and the IRB/EC (see Section 14.3 for record retention information).

11. DISCONTINUATIONS

11.1. Treatment Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the investigational product and/or from the study:

- Adverse event
- Progressive disease
- Symptomatic deterioration (global deterioration of health status)
- Physician decision
- Withdrawal by subject
- Death
- Lost to follow-up
- Protocol violation
- Other (to be specified on CRF)

The reason for discontinuation of treatment should be recorded in the CRF and in the source documents.

The decision to discontinue a subject from treatment remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, prior to discontinuing a subject, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

All subjects discontinued from protocol prescribed treatment for any reason should undergo End of Treatment procedures including a pregnancy test for FCBP. Additionally, all subjects discontinued from protocol prescribed treatment will be followed for a period of 28 days following

the last dose of IP or until the date of the last study visit, whichever is later, for the collection of adverse events.

For subjects who enter survival follow-up in the Follow-up Phase of the study (subjects from parent CC-486 protocol who require survival follow-up): During the survival follow-up in the Follow-up Phase, all subjects should be followed every month for the first year and then every 3 months thereafter until study termination for collection of information on survival, disease relapse, and subsequent therapies, unless the subject has specifically withdrawn consent from further follow-up. The Investigator must make every effort to obtain information regarding the subject's survival status before determining the subject is lost to follow-up.

11.2. Study Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the study:

- Withdrawal by subject
- Death
- Lost to follow up
- Study closure
- Transfer to commercially available and reimbursed CC-486
- Adverse event
- Important protocol deviations
- Other (to be specified in eCRF)

The reason for study discontinuation should be recorded in the CRF and in the source documents.

12. EMERGENCY PROCEDURES

12.1. Emergency Contact

In emergency situations, the Investigator should contact the responsible Clinical Trial Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Clinical Trial Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page). This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on-call Celgene/contract research organization Medical Monitor, who will then contact you promptly.

Note: The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the Clinical Trial Physician(s) or Medical Monitor or designee for emergency calls.

12.2. Emergency Identification of Investigational Products

This is an open-label study; therefore, IP will be identified on the package labeling.

13. REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene, its authorized representative, and Investigator abide by GCP, as described in ICH Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

13.2. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. The Sponsor staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions, including obligations of confidentiality of Sponsor information. The Investigator should maintain a list of Sub-Investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an informed consent form (ICF) and are screened for entry into the study. Subjects who fail study entry/screening must have the reason(s) recorded in the subject's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of CRFs and queries.

The information contained in the protocol and amendments (with the exception of the information provided by the Sponsor on public registry websites) is considered Sponsor's confidential information. Only information that is previously disclosed by Sponsor on a public registry website may be freely disclosed by the Investigator or its institution, or as outlined in the Clinical Trial Agreement. The Sponsor protocol, amendment and IB information is not to be made publicly available (for example on the Investigator's or their institution's website) without express written approval from the Sponsor. Information proposed for posting on the Investigator's or their institution's website must be submitted to the Sponsor for review and approval, providing at least 5 business days for review.

At the time results of this study are made available to the public, the Sponsor will provide Investigators with a summary of the results that is written for the lay person. The Investigator is responsible for sharing these results with the subject and/or their caregiver as agreed by the subject.

13.3. Subject Information and Informed Consent

The Investigator must obtain informed consent of a subject and/or a subject's legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original ICF signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the ICF must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the ICF. The revised ICF signed and dated by the study subject and by the person consenting the study subject must be maintained in the Investigator's study files and a copy given to the study subject.

13.4. Confidentiality

The Sponsor affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). The Sponsor requires the Investigator to permit Sponsor's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed ICF, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

13.5. Protocol Amendments

Any amendment to this protocol must be approved by the Sponsor's Clinical Trial Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

13.6. Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, ICF, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

Investigational product can only be supplied to an Investigator by the Sponsor or its authorized representative after documentation on all ethical and legal requirements for starting the study has

been received by the Sponsor or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the ICF should also be revised.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by the Sponsor and the IRB/EC prior to use.

13.7. Ongoing Information for Institutional Review Board/ Ethics Committee

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected adverse events as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

13.8. Termination of the Study

The Sponsor reserves the right to terminate this study prematurely at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities, etc).

In addition, the Investigator or the Sponsor has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

13.9. Sponsor Commitment to Diversity in Clinical Trials

The mission of the Sponsor is to transform patients' lives through science by discovering, developing, and delivering innovative medicines that help them prevail over serious diseases.

The Sponsor is committed to doing its part to ensure that patients have a fair and just opportunity to achieve optimal health outcomes.

The Sponsor is working to improve the recruitment of a diverse subject population with the goal that the clinical trial becomes more reflective of the real-world population and the people impacted by the diseases studied.

14. DATA HANDLING AND RECORDKEEPING

14.1. Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the IP are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of CRFs or CD-ROM.

14.2. Data Management

Data will be collected via CRF and entered into the clinical database per the Sponsor's Standard Operating Procedures (SOPs). This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

14.3. Record Retention

Essential documents must be retained by the Investigator according to the period of time outlined in the clinical trial agreement. The Investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed ICFs for all subjects;
- Subject identification code list, study entry/screening assessment log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, Celgene, and their authorized representative(s);

- List of Sub-Investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);
- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify the Sponsor if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from the Sponsor prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask the Sponsor for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator or institution should take measures to prevent accidental or premature destruction of these documents.

14.4. Data Protection, Data Privacy, and Data Security

The Sponsor collects and processes personal data of study subjects, patients, health care providers, and researchers for biopharmaceutical research and development to advance innovative, high-quality medicines that address the medical needs of patients. The Sponsor ensures the privacy, protection, and confidentiality of such personal data to comply with applicable laws. To achieve these goals, the Sponsor has internal policies that indicate measures and controls for processing personal data. The Sponsor adheres to these standards to ensure that collection and processing of personal data are limited and proportionate to the purpose for which the Sponsor collects such personal data. This purpose is clearly and unambiguously notified to the individual at the time of collection of personal data. In the true spirit of science, the Sponsor is dedicated to sharing clinical trial information and data with subjects, medical/research communities, the media, policy makers, and the general public. This is done in a manner that safeguards participant privacy and informed consent while respecting the integrity of national regulatory systems. Clinical trial data, health-related research, and pharmacovigilance activities on key-coded health data transferred by the Sponsor across national borders is done in compliance with the relevant data protection laws in the country and GCP requirements.

The Sponsor protects Personal Information with adequate and appropriate security controls as indicated under the data protection laws. To align with the recommended security standards, the Sponsor has adopted internal security standards and policies to protect personal data at every stage of its processing.

To supplement these standards, the Sponsor enters into Clinical Trial Agreements (CTAgs) with confidentiality obligations to ensure proper handling and protection of personal data by third parties accessing and handling personal data.

The Sponsor takes unauthorized access and disclosure of Personal Information very seriously. The Sponsor has adopted the security standards that include National Institute of Standards and Technology Cybersecurity Framework for studies in the US. The Sponsor aligns with these standards to continuously assess and improve its ability to protect, detect, and respond to cyber attacks and other unauthorized attempts to access personal data. These standards also aid in mitigating possible adverse effects. Furthermore, Sponsor Information Technology has defined 6 principles to protect our digital resources and information:

1) Responsibilities of IT Personnel
2) Securing the Sponsor Digital Infrastructure
3) Identity and Access Management
4) External Partner Connections
5) Cyber Threat Detection and Response
6) Internal Cyber Incident Investigation

15. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by the Sponsor or its authorized representative for compliance with applicable government regulations with respect to current GCP and SOPs.

15.1. Study Monitoring and Source Data Verification

The Sponsor ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the Investigator and the staff at a study initiation visit and/or at an Investigators' Meeting. Prior to enrolling subjects into the study, a Sponsor representative will review the protocol, CRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, investigational product storage area, CRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Sponsor representative in accordance with the Study Monitoring Plan.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the CRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the CRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

15.2. Audits and Inspections

In addition to the routine monitoring procedures, a GCP Quality Assurance unit exists within the Sponsor. Representatives of this unit will conduct audits of clinical research activities in accordance with the Sponsor's SOPs to evaluate compliance with GCP guidelines and regulations.

The Investigator is required to permit direct access to the facilities where the study took place, source documents, CRFs and applicable supporting records of study subject participation for audits and inspections by IRB/ECs, regulatory authorities (eg, FDA, European Medicines Agency, Health Canada) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact the Sponsor immediately.

16. PUBLICATIONS

As described in Section 13.2, all protocol- and amendment-related information, with the exception of the information provided by the Sponsor on public registry websites, is considered Sponsor confidential information and is not to be used in any publications. Sponsor protocol-related information proposed for use in a publication must be submitted to the Sponsor for review and approval, and should not be utilized in a publication without express written approval from the Sponsor, or as described in the Clinical Trial Agreement.

The Sponsor will ensure sponsored studies are considered for publication in the scientific literature in a peer-reviewed journal, irrespective of the results. At a minimum, this applies to results from all Phase 3 clinical studies, and any other study results of significant medical importance. This also includes results relating to investigational medicines whose development programs have been discontinued.

Study results may also be presented at one or more medical congresses, and may be used for scientific exchange and teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations.

Eligibility for external authorship, as well as selection of first authorship, will be based on several considerations, including, but not limited to, contribution to protocol development, study recruitment, data quality, participation in data analysis, participation in study steering committee (when applicable) and contribution to abstract, presentation and/or publication development.

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18. APPENDICES

APPENDIX A TABLE OF ABBREVIATIONS

Table 6: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the curve
β-hCG	β-subunit of human chorionic gonadotropin
BID	Twice daily
BSC	Best supportive care
BUN	Blood urea nitrogen
CBC	Complete blood count
CCR	Conventional care regimen
CMML	Chronic myelomonocytic leukemia
COVID-19	Coronavirus disease 2019
CR	Complete remission
CRF	Case report form
CRi	Complete remission with incomplete blood count recovery
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trials Facilitation and Coordination Group
CYP	Cytochrome P450
EC	Ethics Committee
eCRF	Electronic CRF
EEA	European Economic Area
EOT	End of treatment
ESA	Erythropoiesis stimulating agent
EU	European Union
FCBP	Females of childbearing potential
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice

Table 6: Abbreviations and Specialist Terms

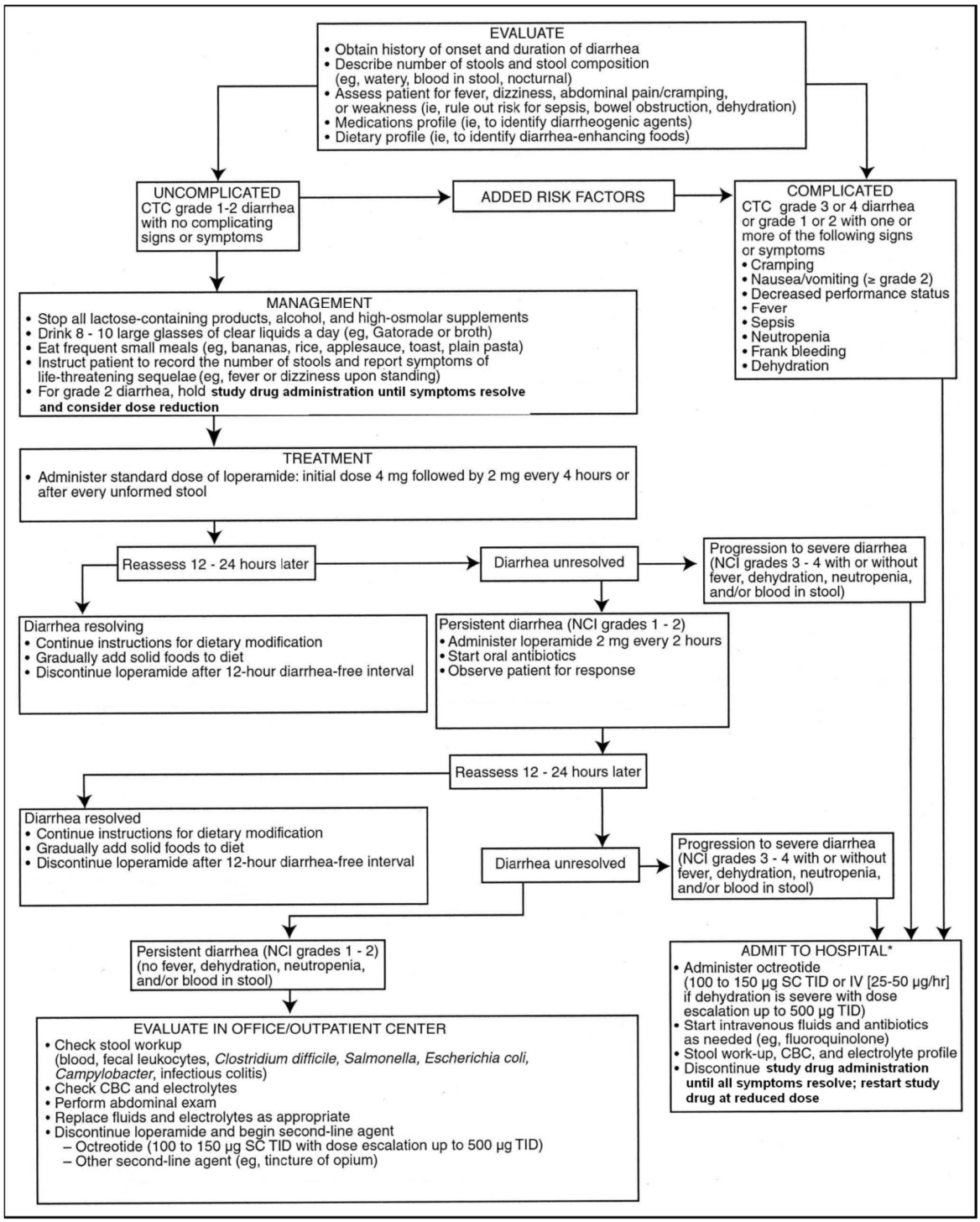
Abbreviation or Specialist Term	Explanation
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte macrophage colony-stimulating factor
HMA	Hypomethylating agents
HR	Hazard ratio
HRT	Hormone replacement therapy
HSCT	Hematopoietic stem cell transplantation
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational medicinal product
IND	Investigational New Drug
INT	Intermediate
IP	Investigational product
IPSS	International Prognostic Scoring System
IRB	Institutional Review Board
IRT	Integrated Response Technology
IUS	Intrauterine hormone-releasing system
IV	Intravenous
LAM	Lactational amenorrhea method
LDAC	Low-dose cytarabine
LDH	Lactate dehydrogenase
MDS	Myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
OS	Overall survival
pRBC	Packed red blood cell
PE	Physical examination
QD	Once daily
RA	Refractory anemia
RAEB	Refractory anemia with excess blasts
RBC	Red blood cell

Table 6: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
RFS	Relapse-free survival
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous
SDev	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
US	United States
WBC	White blood cell
WHO	World Health Organization

APPENDIX B RECOMMENDATIONS FOR MANAGEMENT OF TREATMENT-INDUCED DIARRHEA

Published guidelines (Benson, 2004) were modified for consistency with the study protocol.



Key: CBC = complete blood count; CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NCI = National Cancer Institute; SC = subcutaneous; TID = three times daily.

APPENDIX C FEMALES OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

Appendix C provides general information and definitions related to Females of Childbearing Potential (FCBP) and methods of contraception that can be applied to most clinical trials. For information specific to this study regarding acceptable contraception requirements for female and male subjects, refer to Section 4.2 of the protocol. Only the contraception methods as described in Section 4.2 are acceptable for this study.

DEFINITIONS

Females of Childbearing Potential (FCBP)

A female is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Female in the following categories are not considered FCBP:

- Premenarchal
- Premenopausal female with one of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle-stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause.

Note: Females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. Suggested guidelines for the duration of the washout periods for HRT types are presented below. Investigators should use their judgment in checking serum FSH levels.

- 1-week minimum for vaginal hormonal products (rings, creams, gels)
- 4-week minimum for transdermal products
- 8-week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/mL at any time during the washout period, the woman can be considered postmenopausal.

End of Relevant Systemic Exposure

End of relevant systemic exposure is the time point where the Investigational Medicinal Product (IMP) or any active major metabolites have decreased to a concentration that is no longer considered to be relevant for human teratogenicity or fetotoxicity. This should be evaluated in context of safety margins from the no-observed-adverse-effect level or the time required for 5 half-lives of the IMP to pass.

METHODS OF CONTRACEPTION

Local laws and regulations may require use of alternative and/or additional contraception methods.

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of < 1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation. (This method of contraception can only be used by FCBP subjects in studies where hormonal contraception is permitted by the study protocol.)[b] – Oral (birth control pills) – Intravaginal (rings) – Transdermal • Combined (estrogen-and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy.
• Progestogen-only hormonal contraception associated with inhibition of ovulation. (This method of contraception can only be used by FCBP subjects in studies where hormonal contraception is permitted by the study protocol.)[b] – Oral – Injectable • Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study therapy.
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation. (This method of contraception can only be used by FCBP subjects in studies where hormonal contraception is permitted by the study protocol.)[b] • Intrauterine device. • Intrauterine hormone-releasing system (IUS). (This method of contraception can only be used by FCBP subjects in studies where hormonal contraception is permitted by the study protocol.)[b,c]

- Bilateral tubal occlusion.

- Vasectomized partner

Having a vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the FCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

Male subjects will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with FCBP, even if the subjects have undergone a successful vasectomy or if their partner is already pregnant or breastfeeding.

- Sexual abstinence.

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

- Continuous abstinence must begin at least 30 days prior to initiation of study therapy.
- It is not necessary to use any other method of contraception when complete abstinence is elected.
- FCBP subjects who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the FCBP participant chooses to forego complete abstinence.
- Periodic abstinence (including, but not limited to, calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study.

NOTES:

a Typical use failure rates may differ from failure rates when contraceptive methods are used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects in clinical studies.

b Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.

c IUSs are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness.

Less Than Highly Effective Contraceptive Methods That Are User Dependent

Failure rate of > 1% per year when used consistently and correctly.

- Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously.
- Diaphragm with spermicide.
- Cervical cap with spermicide.

• Vaginal sponge with spermicide. • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action. (This method of contraception cannot be used by FCBP subjects in studies where hormonal contraception is prohibited.**)**
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, postovulation methods). • Withdrawal (coitus interruptus). • Spermicide only. • LAM.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of pregnancy information and outcome of pregnancy on the Pregnancy Report Form or approved equivalent form is provided in Section 10.4.1.