DISCLOSURE

REDACTED STATISTICAL ANALYSIS PLAN

CC-5013-AML-002

A PHASE 2, MULTICENTER, SINGLE-ARM, OPEN LABEL STUDY TO EVALUATE THE ACTIVITY, SAFETY AND PHARMACOKINETICS OF LENALIDOMIDE (REVLIMID®) IN PEDIATRIC SUBJECTS FROM 1 TO ≤ 18 YEARS OF AGE WITH RELAPSED OR REFRACTORY ACUTE MYELOID LEUKEMIA

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STATISTICAL ANALYSIS PLAN

A PHASE 2, MULTICENTER, SINGLE-ARM, OPEN-LABEL STUDY TO EVALUATE THE ACTIVITY, SAFETY AND PHARMACOKINETICS OF LENALIDOMIDE (REVLIMID®) IN PEDIATRIC SUBJECTS FROM 1 TO ≤ 18 YEARS OF AGE WITH RELAPSED OR REFRACTORY ACUTE MYELOID LEUKEMIA

STUDY DRUG: **LENALIDOMIDE (REVLIMID®)**

PROTOCOL NUMBER: **CC-5013-AML-002**

DATE FINAL: **02 Jan 2018**

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on behalf of
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SIGNATURE PAGE

STATISTICAL ANALYSIS PLAN (SAP) and SAP amendment APPROVAL SIGNATURE PAGE	
SAP TITLE	CC-5013-AML-002 Statistical Analysis Plan
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Signature statement	By my signature, I indicate I have reviewed this SAP and find its contents to be acceptable.

Statistical Therapeutic Area Head		
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Lead Product Safety Physicia		
Signature		
Printed Name		Date

1. LIST OF ABBREVIATIONS

Table 1: Abbreviations and Specialist Terms

Abbreviation	Meaning
AE	Adverse Event
Ae	Cumulative Amount of Drug Excreted
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BMA	Bone Marrow Aspirate
BSA	Body Surface Area
CI	Confidence Interval
CLcr	Creatinine Clearance
CL_R	Renal Clearance
CL/F	Apparent Total Clearance
C_{max}	Observed Maximum Concentration
CR	Complete Remission
CRi	Complete Remission with Incomplete blood count recovery
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DAO	Disease Assessment Outcome
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EWOG	European Working Group

Abbreviation	Meaning
fe	Cumulative Percentage of the Administered Dose Excreted
GCP	Good Clinical Practices
GVHD	Graft-Versus-Host Disease
HSCT	Hematopoietic Stem Cell Transplantation
IAF	Informed Assent Form
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IP	Investigational Product
ITT	Intention to Treat
IWG	International Working Group
LDH	Lactate Dehydrogenase
Max	Maximum
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
NCI	National Cancer Institute
OEP	Optional Extension Phase
PK	Pharmacokinetic
PP	Per-Protocol
PR	Partial Remission
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
RBC	Red Blood Cells

Abbreviation	Meaning
rrAML	Relapse or Refractory Acute Myeloid Leukemia
RR	Response Rate
Rsq	Regression Coefficient for Calculation of λz
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SQRT	Square Root
StdDev	Standard Deviation
SOC	System Organ Class
SPM	Second Primary Malignancy
TEAE	Treatment Emergent Adverse Event
TFR	Tumor Flare Reaction
TL	Topline
TLS	Tumor Lysis Syndrome
T_{max}	Time at which Maximum Concentration is Observed
$t_{½}$	Terminal Phase Half-life
TTR	Time to Response
Vz/F	Apparent Volume of Distribution
WBC	White Blood Cells
WHO	World Health Organization
λz	Terminal Phase Rate Constant

2. INTRODUCTION

This statistical analysis plan (SAP) describes the analyses and data presentations for Celgene's protocol CC-5013-AML-002 titled "A phase 2, multicenter, single-arm, open-label study to evaluate the activity, safety and pharmacokinetics of lenalidomide (Revlimid®) in pediatric subjects from 1 to ≤ 18 years of age with relapsed or refractory acute myeloid leukemia", dated 13 Dec 2016. This SAP contains definitions of analysis populations, derived variables and statistical methods for the analyses of efficacy, safety, pharmacokinetic .

These analyses include the interim analysis, the primary final analysis and the end of study final analysis at the close of study.

The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to the analysis of study data prior to database lock and any data analysis for the interim/primary final analysis/end of study final analyses. This SAP is developed after the finalization of the protocol and will be finalized and signed at a minimum 6 weeks prior to the clinical database lock. All statistical analyses detailed in this SAP will be conducted using SAS® Version 9.1 or higher. The clinical cutoff date will be determined based on the completion of stage 1 for the interim analysis (enrollment of 18 subjects) and on completion of stage 2 (enrollment of 43 subjects) for the primary final analysis of the primary endpoint (morphologic complete response rate within the first four cycles of lenalidomide) and other endpoints defined in the protocol. All subjects will be observed until the end of the treatment and will continue to be followed for second primary malignancies (SPM), safety issues (any drug-related SAEs),), start of new anticancer therapies, and transition to hematopoietic stem cell transplantation (HSCT) for up to 5 years after the last subject first dose of lenalidomide, regardless of new anticancer treatment or HSCT.

The following analyses will be performed:

- Periodic reports (at least semi-annually) will be provided to an external data monitoring committee (DMC). The first DMC meeting will be held after 4 subjects have completed at least 1 cycle of study treatment, if having not stopped therapy earlier due to a safety issue, in order to evaluate safety and provide a recommendation.
- An interim analysis will be conducted once 18 evaluable subjects will have completed their Cycle 4 assessments, or will have met discontinuation criteria, whichever occurs first.
- Primary final analysis will be conducted when all on treatment subjects will have completed their Cycle 4 assessments or will have met discontinuation criteria, whichever occurs first.
- End of study final analysis will be performed once all subjects will have discontinued the follow-up period (up to 5 years after the last subject first dose of lenalidomide).

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective of the study is to determine the activity of lenalidomide in the treatment of pediatric subjects with relapsed or refractory acute myeloid leukemia (rrAML) (with second or greater relapse or refractory to at least 2 prior induction attempts) measured by morphological complete response defined as either a CR (Complete Remission) or CRi (Complete Remission with Incomplete blood count recovery) within the first 4 cycles of treatment.

3.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate subject demographics and leukemic blast characteristics and their correlation with response to lenalidomide.
- To further evaluate lenalidomide activity with regards to response assessment outcome rates, transplantation rate and durable response rate.
- To evaluate the safety of lenalidomide including rates of graft-versus-host disease (GVHD) flare and reactivation.
- To determine the pharmacokinetics (PK) of lenalidomide in plasma.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a multicenter, open-label, single-arm, Phase 2, Simon's Optimal two-stage design study, with an Optional Extension Phase (OEP), that will assess the activity, safety and PK of lenalidomide in pediatric subjects from 1 to ≤ 18 years of age with second or greater rrAML. A total of 43 evaluable subjects (18 subjects in Stage 1 and an additional 25 subjects in Stage 2) are required for assessment of the primary endpoint. To allow for subjects found to be unevaluable for the primary endpoint due to an incorrect diagnosis, not having a disease assessment post screening, or who discontinued prior to receiving lenalidomide, up to 4 additional subjects may be enrolled for a maximum of 47 evaluable subjects across approximately 75 sites. Approximately 50% of enrolled subjects will be younger than 12 years of age to provide adequate PK data for this age subset.

If during Stage 1, at least 3 of 18 subjects achieve a morphologic complete response (either CR or CRi) within the first 4 cycles of study treatment, then the study will proceed to Stage 2; otherwise, the study will be terminated. Similarly, if at the primary final analysis, at least 8 of 43 evaluable subjects across Stages 1 and 2 achieve a response (CR/CRi) within the first 4 cycles of study treatment, it will be concluded that lenalidomide has sufficient activity in pediatric acute myeloid leukemia (AML) to warrant subsequent study.

Morphological response will be assessed using the modified AML International Working Group (IWG) criteria (Cheson, 2003) (section 18.1).

The OEP will allow subjects who demonstrate clinical benefit, as assessed by the Investigator at the completion of 12 cycles of lenalidomide therapy, to continue receiving oral lenalidomide until they meet the criteria for study discontinuation. In the OEP, only safety, dosing, concomitant medications/procedures, and SPMs will be monitored.

An external independent data monitoring committee (DMC) will evaluate safety and treatment efficacy data in an ongoing, periodic manner to assess benefit-to-risk considerations throughout the study. The function of the DMC is to monitor the safety and activity of the study treatment. After 4 subjects have completed at least 1 cycle of study treatment, the DMC will evaluate the safety data and provide a recommendation. The DMC will also provide recommendations about the continuation of the study from Stage 1 to Stage 2 (continue as planned, continue with modifications or stop treatment and/or enrollment) and advise on ways to improve quality. The DMC responsibilities, authorities, and procedures will be documented in the DMC charter, which will be endorsed by the DMC prior to the first data review meeting.

The study will consist of 3 phases: Screening Phase, Treatment Phase and Follow-up Phase.

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

Screening Phase

The Screening Phase will start from the time of signing the informed consent form (ICF)/informed assent form (IAF) and will last no more than 14 days, at which time the

Treatment Phase will begin (Cycle 1 Day 1). Subject's screening procedures are to occur during the Screening Phase within 14 days prior to dosing on Cycle 1 Day 1.

Treatment Phase

The lenalidomide dose will be calculated based on body weight. The starting dose will be 2 mg/kg/day with a maximum dose of 70 mg/day. Subjects enrolled in the study will receive lenalidomide for the first 21 days of each 28-day treatment cycle for up to a maximum of 12 cycles of study treatment. After the completion of 12 cycles of study treatment, subjects who demonstrate clinical benefit (CR/CRi/PR) or resistant disease as per the Investigator may continue to receive lenalidomide in an OEP until they meet the criteria for study discontinuation.

In the event of a specific protocol-defined toxicity, no more than 2 dose reductions will be allowed to doses of 1.4 mg/kg/day (not exceeding 50 mg/day) and 1 mg/kg/day (not exceeding 35 mg/day). The dose will not be re-escalated once it has been reduced. Subjects who do not tolerate the minimum dose level of 1 mg/kg/day (not exceeding 35 mg/day) will be discontinued from the study.

Follow-up Phase

Subjects will enter the Follow-up Phase at the time of permanent discontinuation of the investigational product (IP) and will be followed for up to 5 years from the last subject's first dose, unless the subject dies, withdraws consent or is lost to follow-up. The Follow-up Phase may not be terminated because of new anticancer treatment or HSCT.

The 28-day Follow-up Visit will occur 28 days after the subject's last dose of IP. At this visit, subjects will be monitored for the collection of AEs and concomitant medications/procedures used to treat the AEs. Female Children of Childbearing Potential (FCCBP) and Females of Childbearing Potential (FCBP) will have a pregnancy test at the 28-day Follow-up Visit.

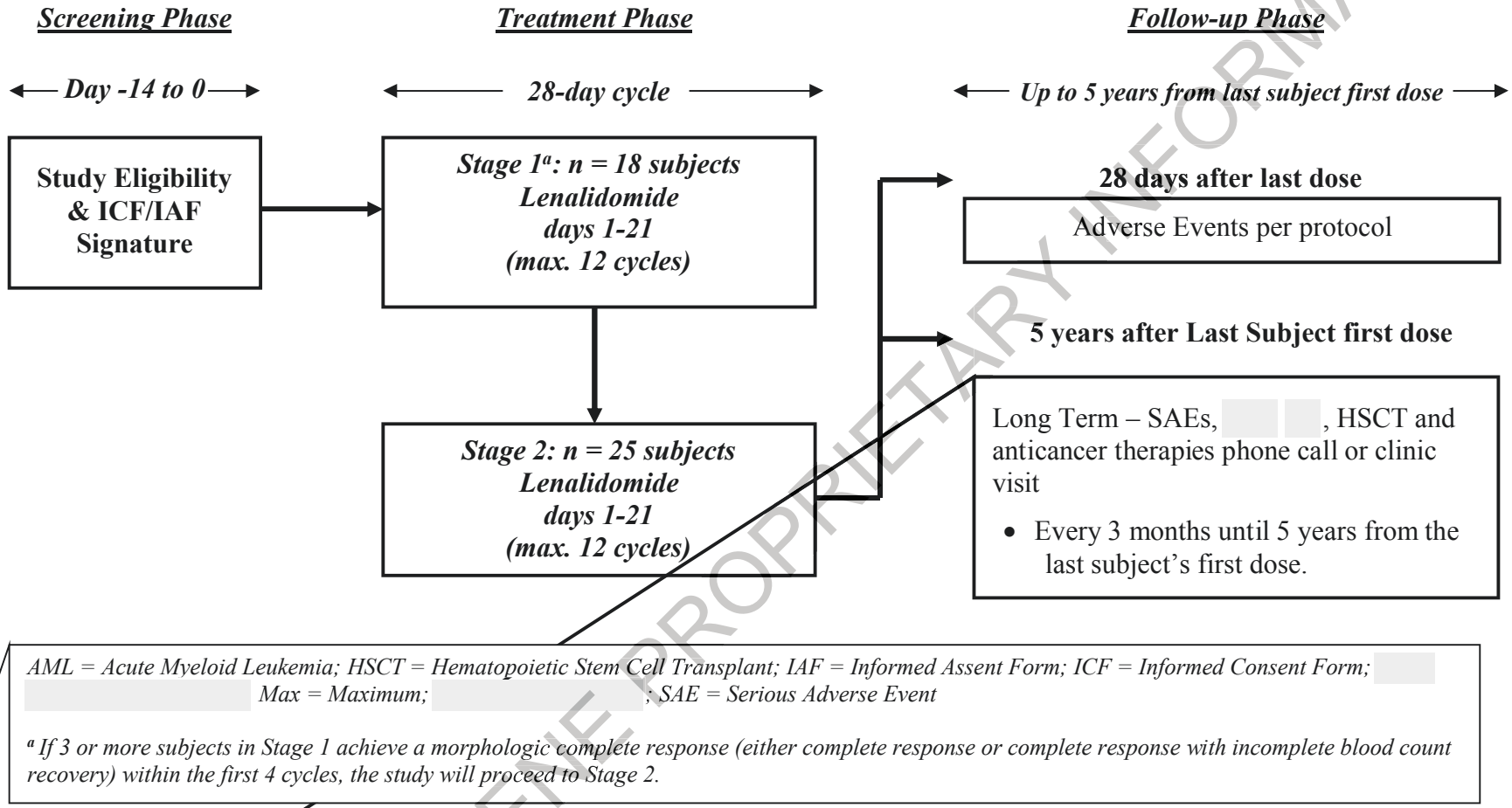
After the 28-day Follow-up Visit, subjects will be followed up by phone or clinic visit, whichever is the institution's normal standard of care, every 3 months for a maximum of 5 years from the last subject's first dose, regardless of new anticancer treatment or HSCT, for SPMs, safety issues (any drug-related SAEs), start of new anticancer therapies, and transition to HSCT.

Optional Extension Phase

Upon completion of 12 cycles of lenalidomide therapy per protocol, subjects who are demonstrating clinical benefit as assessed by the Investigator and who do not meet any of the criteria for treatment discontinuation may enter the OEP.

The study schematic is presented in Figure 1.

Figure 1: Overall Study Design



AML = Acute Myeloid Leukemia; HSCT = Hematopoietic Stem Cell Transplant; IAF = Informed Assent Form; ICF = Informed Consent Form; Max = Maximum; ; SAE = Serious Adverse Event

[a] If 3 or more subjects in Stage 1 achieve a morphologic complete response (either complete response or complete response with incomplete blood count recovery) within the first 4 cycles, the study will proceed to Stage 2.

4.2. Study Endpoints

4.2.1. Primary Endpoint

The primary endpoint is the morphologic complete response rate (CR or CRi) within the first 4 cycles of treatment with lenalidomide based on the modified IWG AML response criteria (Cheson, 2003, see Section 18.1).

4.2.2. Secondary Endpoints

The secondary endpoints of the study are the following:

- Time to response.
- Durable response rate based on the revised AML IWG Criteria (Cheson, 2003, see Section 18.1).
- Disease assessment outcomes and overall response rate (ORR).
- Rate of hematopoietic stem cell transplant (HSCT).
- Incidence and severity of treatment-emergent adverse events (TEAEs).
- Rates of acute and chronic graft-versus-host disease (GVHD).
- Plasma pharmacokinetic (PK) parameters including lenalidomide apparent clearance and volume of distribution.
- Correlation of peripheral white blood cell count, absolute blast count and cytogenetics with response to lenalidomide.

4.3. Stratification , Randomization, and Blinding

This is a single arm study with no randomization, blinding, or stratification planned in the study design.

4.4. Sample Size Determination

Under Simon's Optimal two stage design with a 5% significance level and 80% power, assuming a lower boundary of interest in the response rate of 10% and an upper boundary of interest in the response rate of 25%, a total of 43 evaluable subjects are required for the evaluation of the primary endpoint; 18 in Stage 1 and an additional 25 in Stage 2.

If less than 3 of 18 evaluable subjects in Stage 1 achieve a morphologic response (either CR or CRi) within a maximum of 4 cycles then the study will terminate, otherwise the study shall continue as planned and enrollment of an additional 25 subjects shall continue into Stage 2.

If, at the primary final analysis, less than 8 of 43 evaluable subjects in both Stage 1 and 2 achieve a response (either CR or CRi) within a maximum of 4 cycles then it will be concluded that lenalidomide, at the dose level tested, does not have sufficient activity in pediatric AML (second or greater relapse or refractory). However, should at least 8 of the 43 evaluable subjects achieve a response (either CR or CRi) then it will be concluded that lenalidomide, at the dose level tested, demonstrates activity in pediatric subjects with AML (second or greater relapse or refractory) to allow further investigation. Up to 4 additional subjects may be included to account for subjects found to be unevaluable for the primary endpoint (eg, incorrect diagnoses, not having a disease assessment post screening, or who discontinued prior to receiving lenalidomide therapy). The first 43 subjects enrolled and evaluable for the primary final analysis will be used to assess the primary endpoint.

5. GENERAL STATISTICAL CONSIDERATIONS

5.1. Reporting Conventions

The summary tables, listings, and any supportive SAS output will include the explanatory "headers" that indicate, at a minimum:

- protocol number
- data cutoff date
- company name (Celgene Corporation)
- page number (Page x of x)

The Summary tables, listings, and any supportive SAS output will include the explanatory "footers" that indicate, at a minimum:

- program source (ie, SAS program name, including the path, run date)
- data extraction date
- data source (ie, list of datasets used for the display)

The purpose of the data extraction date is to link the output to the database, either active or archived, that is write-protected for replication and future reference. The program run date is the output date which will appear on each output page and will indicate the date the output was generated by the analysis program. Individual source listings will display all the relative values supporting corresponding table(s) and figure(s).

In addition, the following reporting conventions will be implemented:

- Data from all study centers will be combined for analysis;
- Confidence intervals (CIs) will be presented as 2-sided 95% CIs unless otherwise specified;
- Summary statistics will consist of the number and percentage of subjects in each category for discrete variables, and the sample size, mean, median, standard deviation (StdDev), first quartile (Q1), third quartile (Q3), minimum (Min), and maximum (Max) for continuous variables;
- All mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value;
- All percentages will be rounded to one decimal place. The number and percentage of responses will be presented in the form xx (xx.x), where the percentage is in the parentheses. In the case the numerator is equal to the denominator, the percentage should be presented as (100) instead of (100.0);
- All listings will be sorted for presentation in order of study center, subject, and date of procedure or event;

- All analysis and summary tables will have the analysis population sample size (ie, number of subjects) wherever applicable;
- Baseline is defined as the latest value collected on or before the date when the first dose of study treatment is administered. If multiple values are present for the same date, the mean of these values will be used as the baseline, with the exception of lab data where the value with the worst Common Terminology Criteria for Adverse Events (CTCAE) grade will be set as baseline. For subjects who were not treated, the baseline value will be defined as the latest value collected on or prior Day 1 of the Cycle 1 visit if available.

5.2. Calculation of Treatment Start Dates, Cycles, and Treatment End dates

Treatment will commence on Day 1 and planned cycle lengths are 28 days. Day 1 of treatment is defined as the first day of study drug. Day 1 of a cycle is defined as day 1 of study drug for the given cycle as recorded on the eCRF.

Cycle end dates are defined as the day before Day 1 of the following cycle. The treatment end date, and the end date of the last cycle, will be calculated as follows:

- For subjects who discontinue prior to the clinical cutoff date, treatment end date is the date of treatment discontinuation from the treatment disposition page in the eCRF;
- For subjects who are still on treatment at the time of study closure or clinical cutoff, the last date of planned cycle (27 days after first dose of the last cycle) will be used as the treatment end date.

The cycle number for each date of interest, e.g. Adverse Event (AE) start date, will be calculated based on the cycle window set by their start and end dates.

The following rules will be implemented for cycle calculations for Treatment-Emergent AEs (TEAEs):

- TEAEs present on or after Day 1 Cycle i but before Day 1 of the subsequent Cycle belong to Cycle i;
- All TEAEs which occur after Day 1 of the last cycle will be included only in the last cycle.

5.3. Study Population Definitions

5.3.1. Informed Consent/Assent Population

Informed consent/assent population will consist of all subjects with signed informed consent/assent.

5.3.2. Response Rate Population

The response rate (RR) population shall consist of all subjects classified as evaluable for the primary endpoint, ie, all subjects fulfilling the eligibility criteria, having received at least one dose of the lenalidomide and having at least one disease IWG response assessment post

enrollment or having treatment failure (as assessed in the "Disposition - Treatment" eCRF page) before an assessment can be conducted. The RR population shall be applied to the analysis of the primary endpoint.

5.3.3. Intention-to-Treat Population

The intention to treat (ITT) population shall consist of all enrolled subjects regardless of whether they received lenalidomide. The ITT population will be used for the analysis of all efficacy-based endpoints and for listings if not otherwise specified.

5.3.4. Safety population

The safety population consists of all subjects receiving at least one dose of lenalidomide and shall be applied to all safety based endpoints.

5.3.5. Pharmacokinetic Population

The PK population consists of all subjects receiving at least one dose of lenalidomide and having at least one measurable lenalidomide concentration. The PK population shall be used for analysis of PK data.

6. SUBJECT DISPOSITION

Subject disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency counts and percent for each phase of the study.

Subjects completing the Screening Phase and reasons for screen failures, as collected in the eCRF page "Disposition - Screening" will be presented for all screened subjects (defined as subjects having a signed ICF/IAF) using the following categories:

- Completed
- Screen failure
- Death
- Adverse Event
- Withdrawal by subject
- Lost to follow-up
- Withdrawal by parent/guardian
- Other
- Missing

Completed subjects and reasons for treatment discontinuation during the fixed Treatment Phase as recorded in the "Disposition - Treatment" eCRF page will be summarized for intention to treat subjects with the following categories:

- Completed
- Death
- Adverse event
- Withdrawal by subject
- Lost to follow-up
- Withdrawal by parent/guardian
- Pregnancy
- Non-compliance with study drug
- Physician decision
- Protocol violation
- Other
- Missing

Subjects completing the study OEP/Follow-up Phase and reasons for not completing it will be collected on the eCRF ("Disposition - Treatment OEP" or "Disposition - Follow-up" pages) and will be summarized for all intention to treat subjects with the following categories in two separate tables:

- Completed
- Death
- Adverse event*
- Withdrawal by subject
- Lost to follow-up
- Withdrawal by parent/guardian
- Pregnancy*
- Non-compliance with study drug*
- Physician decision*
- Protocol violation*
- Other
- Missing

*Not applicable to the Follow-up Phase.

Table for the OEP phase will report disposition only for subjects who will have entered the OEP treatment period.

Analysis population allocation will be tabulated and listed. A summary of subjects enrolled by site will be provided.

Listings will be provided about patient disposition for all periods after the treatment start (first 12 cycles, optional extension phase, follow-up), for subjects who failed eligibility criteria and for subjects with previous participation to the study screening.

7. PROTOCOL DEVIATIONS/VIOLATIONS

The protocol deviations/violations will be identified and assessed by the clinical monitor of the sponsor or designee following company standard operational procedure: these possible deviations and violations are entered into the clinical trial management system by the clinical monitor and are reviewed by the sponsor for confirmation/correction. This adjudicated file will be used for analysis.

The protocol violations will be summarized for the ITT population using frequency tabulations. Moreover frequencies will be provided for number of subject with one, two or more than two protocol violations.

A listing of subjects with protocol violations/deviations in the ITT population will be provided.

8. BACKGROUND AND DEMOGRAPHIC CHARACTERISTICS

The demographics and baseline characteristics will be summarized in the ITT population. Individual subject listings will be provided to support the summary tables.

8.1.1. Demographics

The following demographics will be summarized descriptively:

- Age (years)
- Sex
- Race
- Ethnicity
- Reproductive Status
- Weight (kg)
- Height (cm)

For age, also frequency counts and percentages for the following categories will be presented: ≤ 2, 3-6, 7-12, 13-16, 17-18 years. Years reached are to be used for categorization.

During calculation of age, when day of birth is missing (e.g. for regulatory authority directions) impute first day of the month, as requested in Section 18.3.1. Both ages, computed and collected in the eCRF, will be summarized.

Listing will be provided for demographic characteristic. Within listings, age will be displayed in years and months as computed following directions given in Section 18.3.1 while within tables summary statistics for age in years will be used.

8.1.2. Baseline Characteristics

The following baseline clinical characteristics will be summarized descriptively:

- Lansky and Karnofsky performance score (for subjects ≤ 16 and > 16 years of age, respectively)
- Baseline electrocardiogram (ECG)
- Vital Signs (with respiratory rate)
- White blood cell count
- Absolute blasts
- Absolute neutrophils
- Platelets
- Peripheral blood smear blasts
- Bone marrow differential

8.1.3. Medical History

All medical history, up to 5 years before ICF/IAF signature, will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). The version of the MedDRA will be indicated in the footnote of relevant tables based on the current version used in the clinical data.

A summary of medical and surgical history will be presented by MedDRA system (Version 18.0 or higher) and system organ class (SOC) and preferred term (PT). A similar summary will be generated for the currently active abnormalities only, by SOC and PT. Listing will be provided for the ITT population.

Prior cancer history will also be summarized and listed as collected in the "Prior Cancer History Question", "Prior Cancer History" and "Prior Cancer History II" pages of eCRF.

8.1.4. Prior and Concomitant Medications/Procedures

Medications reported on the eCRF will be coded to therapeutic drug classes and generic drug names using Anatomical Therapeutic Chemical (ATC) coding scheme of the World Health Organization (WHO) drug dictionary (WHO-DDE March 2015 will be the initial version used, with subsequent eventual updates). Medications/procedures will be recorded from the time of the signing of informed consent/assent (medications within 14 days) until 28 days after the last dose of the IP. All prior medications/procedures related to AML or any malignancy, and received at any point in subjects history should be recorded on the CRF at screening, regardless of time.

Medications initiated prior to the start of study treatment and continued after the start of study treatment will be counted as both prior and concomitant medications. In the occurrence of partial dates, refer to Appendix 18.4 where the date imputation guideline is located.

A summary showing the number and percentage of subjects who took prior/concomitant medications will be presented by WHO therapeutic drug class and generic drug name. Therapeutic drug class and generic drug name will be listed in alphabetical order. A separate summary showing the number and percentage of subjects who underwent prior/concomitant procedures will be presented by MedDRA SOC and PT. SOC and PT will be listed in alphabetical order. Prior medication/procedure summaries will be presented for the ITT population while concomitant medication/procedure summaries will be presented for safety population.

A complete list of all prior and concomitant medications (prescription, over the counter, nutritional, fiber supplements, etc.), indication/diagnosis, dose, dosing regimen (frequency, route), and start and stop dates used prior to and during the study will be reported. A separate complete list of all prior and concomitant procedures, indication and date of procedure or surgery will be reported.

8.1.4.1. Prior Medications/Procedures

Prior medications and procedures are defined as medications and procedures starting before the start of the study treatment and either ending before the start of the study treatment or continuing after study treatment start. A summary showing the number and percentage of subjects who took prior medications will be presented for the ITT population.

Prior medications collected on the "Prior/Concomitant Medication" eCRF page and prior procedures collected on the "Prior/Concomitant procedures" eCRF page will be summarized.

Medications/procedures collected on the "Prior Radiation Therapies", "Prior Cancer Surgeries for this Disease", "Prior Hormonal Anti-Cancer Therapies for this Disease", "Prior Systemic Anti-Cancer Therapies", "Procedures for Prior Cancers Not Under Study", and "Radiation Treatment For Prior Cancers Not Under Study" eCRF pages will be summarized for the safety population and listed for the ITT population.

8.1.4.2. Concomitant Medications/Procedures

Concomitant medications and procedures are defined as medications and procedures either initiated before the first dose of study drug and continuing during the study treatment, or initiated between first date of first dose of study drug and 28 days from the date of last dose of study medication.

Concomitant medications collected on the "Prior/Concomitant Medication" eCRF pages and concomitant procedures collected on the "Prior/Concomitant procedures" eCRF page will be summarized for the safety population.

A separate listing will be provided for data collected in the "Intrathecal Cytarabine" eCRF page and "Stem cell transplant" eCRF page for the ITT population.

9. STUDY TREATMENT AND EXTENT OF EXPOSURE

All study treatment and extent of exposure summaries will be provided based on the RR and safety populations. Descriptive statistics will be provided for treatment duration, average weekly dose, number of cycles, cumulative dose, dose intensity, relative dose intensity, treatment exposure and dose reductions / interruptions. Study drug record will be presented in a listing for the safety population.

The fixed Treatment Period and OEP treatment period will be considered together as a unique period for exposure analysis. In addition, summary statistics for treatment duration and dose information will be provided only for subjects that enter the OEP treatment phase and is limited to the OEP period.

9.1. Treatment Duration

Treatment Duration (weeks) is defined as:

[(date of end of treatment) – (date of first treatment) + 1]/7

Date of first treatment is defined as the date of the first non-zero dose of lenalidomide administered for each phase, fixed phase and OEP phase.

Date of end of treatment is defined as follows:

- For subjects who completed 12 (or more if the subject entered the OEP of treatment) full cycles of lenalidomide, the end of lenalidomide is defined as Day 28 of last completed cycle 12.
- For subjects not considered in the previous point and for subjects who prematurely discontinued lenalidomide before day 21 of the cycle, the end of lenalidomide is the date either the investigator or subject decided to prematurely discontinue lenalidomide, which is referred to as “Date of Completion/Discontinuation” recorded on the eCRF page called “Disposition - Treatment” (or “Disposition - Treatment OEP” if the subject entered the OEP of treatment).

Descriptive statistics will be provided for treatment duration (n, Mean, StdDev, Median, Q1, Q3, Min, Max), total number of cycles completed (frequency count); if a subject has completed the 21 treatment days, the cycle will be considered completed. In addition, summary statistics will be provided only for subjects that enter the OEP treatment phase and limited to the OEP period.

9.2. Cumulative Dose

Cumulative dose of lenalidomide will be computed as the sum of all doses administered, defined as the values entered on the actual dose assigned field on the dosing eCRF, taken across the treatment period (including OEP). Cumulative dose will be in mg/kg for all subjects.

Descriptive statistics will be presented for cumulative dose for subjects in the RR and safety population. Tabulations will be presented as dose information, by cycle and overall separately. In addition, for the OEP overall (ie all OEP cycles together) period, summary statistics will be provided for subjects that will enter the OEP treatment phase.

9.3. Dose Exposure

Dose exposure in weeks is defined as the total number of actual days on drug during the treatment period divided by 7. Descriptive statistics will be presented for dose exposure for subjects in the RR and safety population. Tabulations will be presented as dose information, by cycle and overall separately. In addition, for the OEP overall period, summary statistics will be provided for subjects that will enter the OEP treatment phase.

9.4. Average Weekly Dose

Average weekly dose will be calculated as the cumulative dose in mg/kg divided by dose exposure in weeks. Descriptive statistics will be presented for average weekly dose for subjects in the RR and safety population. Tabulations will be presented as dose information, by cycle and overall separately. In addition, for the OEP overall period, summary statistics will be provided for subjects that will enter the OEP treatment phase.

9.5. Dose Intensity

Dose intensity during the treatment is defined as the cumulative dose in mg/kg divided by the treatment duration in weeks.

Dose intensities will be calculated as follows: Dose intensity (mg/kg/weeks) = [cumulative dose for lenalidomide in mg/kg]/[treatment duration in weeks].

Dose intensity will be presented as dose information, by cycle and overall separately, for the treatment period of the study for the response rate and safety populations. In addition, for the OEP overall period, summary statistics will be provided for subjects that will enter the OEP treatment phase.

9.6. Relative Dose Intensity

Relative dose intensity is the dose intensity divided by the protocol specified weekly dose (both expressed as mg/m^2/week), expressed as a percentage:

Relative dose intensity (%) = (dose intensity / protocol weekly dose) * 100%
where protocol weekly dose (the planned dose intensity) is the mean of the expected weekly doses (14 mg/kg/week) of all cycles of treatment initiated by the subject.

Relative dose intensity of lenalidomide will be categorized into <70%, ≥70% to < 80%, and ≥80 to <90% and ≥90%, and frequency counts will be provided together with summary statistics for the RR and safety population and will be tabulated together with overall dose information. In addition, summary statistics will be provided only for subjects that enter the OEP treatment phase and limited to the OEP period.

9.7. Exposure and Dose Reduction/Interruption

Dose reduction/interruption due to AE and other reasons will be summarized. A dose reduction is defined as any non-zero reduced dose of lenalidomide with AE or any other reason recorded on the eCRF page "Study Drug Record". Dose interruption is defined as any zero dose of lenalidomide with AE or any other reason recorded on the eCRF.

If an interruption happens at the start of a cycle and causes the cycle to be delayed, it is also called a dose delay. A maximum delay of 2 weeks in the start of cycle will be allowed. For example subjects treated with lenalidomide at Cycle 1 should start the second cycle of treatment no later than 42 days after cycle Day 1 of Cycle 1. Dose delays will be considered together with dose interruptions.

Dose Interruption Criteria:

- Lenalidomide will be held for any subject experiencing hemorrhagic or bullous skin rash until a specific evaluation to exclude toxic epidermal necrolysis and/or Stevens-Johnson syndrome has been performed. Any subject with evidence of toxic epidermal necrolysis or Stevens-Johnson syndrome will not be retreated with lenalidomide.
- Guidelines for GVHD as reported in the protocol section 8.2.1 in "Special Instructions for Management of Graft Versus Host Disease (GVHD)" paragraph.

Dose Reduction:

- Two dose reductions will be allowed (Table 2) in the event of specific protocol-defined toxicity. If treatment is interrupted for toxicity as described below, lenalidomide will be resumed at dose level -1 once the toxicity has resolved to ≤ Grade 1. If toxicity recurs, lenalidomide will be interrupted and upon resolution, the subject will resume at dose level -2.
- The dose will not be re-escalated if the lower dose is tolerated.
- Subjects who do not tolerate 1 mg/kg/day (dose level -2) will discontinue lenalidomide administration.

Table 2: Dose Reductions of Lenalidomide

Dose Level	Dose
Starting dose	2.0 mg/kg/day (maximum dose of 70 mg/day for subjects ≥ 35 kg)
Dose Level -1	1.4 mg/kg/day (not exceeding 50 mg/day for subjects initially dosed at 70 mg/day)
Dose Level -2	1.0 mg/kg/day (not exceeding 35 mg/day for subjects initially dosed at 70 mg/day)

The total number of cycles received and the overall number of dose reductions/interruptions for lenalidomide will be presented. The overall number and percentage of subjects who have at least one dose reduction/interruption for lenalidomide will be provided for each reason. Time to first dose reduction/interruption due to any reason will be descriptively provided. Time to first dose reduction/interruption due to AE will also be descriptively provided. Computation of similar summary statistics and frequency counts will be repeated by cycle and presented in a separated table.

The cycle when the dose reduction/interruption due to AE for lenalidomide, defined as the cycle number during which the dose of lenalidomide was reduced/interrupted due to AE, will be summarized as frequencies within the 4 categories: 1, 2, 3, and >3 cycle.

9.8. Overdose

Overdose, as defined in the protocol, refers to lenalidomide dosing. On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of lenalidomide assigned to a given subject, regardless of any associated AEs or sequelae: >10% 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 any overdose, regardless of whether the overdose was accidental or intentional, will be collected on the eCRF page "Investigational Drug Overdose" and will be presented in a listing.

10. EFFICACY ANALYSIS

Efficacy analyses for the primary endpoints will be performed on the RR and ITT population. Secondary efficacy endpoints will be analyzed for the ITT population.

Data listings will be provided for all endpoints, including bone marrow sample collection and assessment. Moreover bone marrow assessment performed at screening for diagnosis confirmation will also be listed.

10.1. Analysis of Primary Efficacy Endpoint

The primary endpoint is the morphological complete response rate within a maximum of 4 cycles of treatment. Morphological complete response is defined as CR or CRi as assessed locally and reported in the "Modified IWG Response Assessment" eCRF page. These response criteria will be assessed according to the revised AML IWG Criteria (Cheson, 2003, see Section 18.1).

The morphological complete response rate is defined as the total number of subjects with morphological complete response observed within the first 4 cycles of study therapy (regardless of whether the CR/CRi is observed at the end of Cycle 1, 2, 3 or 4) over the total number of subjects evaluable for this endpoint. The CR/CRi does not need to be present at the end of Cycle 4 if observed before this time for the subject to be considered as having achieved a complete response with regards to the primary endpoint. Responses occurring after a treatment failure assessment outcome will not be considered. The corresponding Clopper Pearson 95% confidence interval will be calculated for the response rate.

The primary analysis of this endpoint will be based upon the ITT population and the RR population.

Data as collected in the "Modified IWG Response Assessment" eCRF page will be listed.

10.2. Analysis of Secondary Efficacy Endpoints

Secondary efficacy endpoints will be analyzed and reported based on subjects in the ITT population, if not otherwise specified. All secondary efficacy endpoints will be analyzed at the time when the primary endpoint is due for analysis.

10.2.1. Time to Response

Time to response (TTR) is defined as the time from treatment start until a documented disease response (either CR, CRi or PR). Subjects not observed with a response will not be included in the analysis. Summary statistics (n, mean, StdDev, median, Q1, Q3, min, max) will be provided for time to response.

10.2.2. Overall Response Rate

Overall response rate defined as the proportion of subjects with best response (CR, CRi or PR) among all subjects in the ITT population (i.e. subject will be considered as having a response if they achieve at least PR). Subject achieving less than PR (i.e. 'treatment failure') or having no assessment will be considered as a non-responder. If a subject is missing some assessments, their best response from available assessments will be selected as the response. Responses occurring after a treatment failure will not be considered. All assessments collected while a subject is under study treatment (incorporating, wherever applicable, the 28 day rule, i.e. last dose plus 28 days) will be considered.

The ORR formula will be the following

ORR = (number of CR, CRi or PR from start to the end of period under analysis) / (number of subjects within the ITT population).

The ORR rate at the end of Cycles 1, 2, 3, 4, 8 and 12 will be categorized, and the rate will be calculated for each cycle dividing the number of subjects with response in the cycle by the number of subjects entering the cycle. The formula will be the following

$ORR\ cycle_i$ = (number of CR, CRi or PR form start of Cycle i to the end of Cycle i) / (number of subjects entering Cycle i within the ITT population).

Proportions will be presented as percentages with frequency counts together with the Clopper-Pearson 95% CI, at the end of each pre-specified cycle.

10.2.3. Disease Assessment Outcome

Disease assessment outcome (DAO) at the end of Cycles 1, 2, 3, 4, 8 and 12 of lenalidomide administration shall be categorized according to the Cheson criteria (Cheson, 2003, see Section 18.1) into the following categories: CR, CRi, PR, Treatment Failure (Resistant Disease, Aplasia, Indeterminate Cause, Relapse after CR or CRi, Molecular or Cytogenetic relapse), Missing/not done. Responses occurring after a treatment failure will not be considered. The DAO rate for each of the response criteria will be calculated as the total number of subjects in a given response category at each time point over the number of subjects entering each corresponding cycle. The formula will be the following:

DAO category cycle$_i$ = (number of subjects with DAO category from start of Cycle i Day 1 to the end of Cycle i) / (number of subjects entering Cycle i within the ITT population)*100.

Proportions will be presented as percentages with frequency counts together with the Clopper-Pearson 95% CI, per response category at the end of each pre-specified cycle.

10.2.4. Durable Response Rate

Durable response rate is defined as the proportion of subjects achieving a bone marrow confirmed CR/CRi, as collected in the Modified IWG Response Assessment page of the eCRF, lasting at least 3 months (from time complete response observed until treatment failure or worse) or until transplantation if earlier among all subjects eligible for durable response rate analysis (all ITT population subjects that achieve at least a CR or CRi, provided the CR/CRi is confirmed in a bone marrow sample).

A durable response is a response, either CR or CRi, maintained for at least three cycles (or 84 days) from the first time a response is observed, either CR or CRi whichever occurs first. Durable response occurs when the responses assessed thereafter the first observed CR/CRi are either CR or CRi until at least 84 days after the first observed CR/CRi. If the subject undergoes a transplant before 84 days, the subject will be considered as having achieved a durable response. A CR or CRi observed after a PR or treatment failure will not be considered. If a subject has a PR or treatment failure directly following a missed assessment(s) then consider only up to the last completed assessment prior to the missed assessment(s). Should only one assessment be missing (i.e. no consecutive missing assessment) and the next available assessment directly following the missing assessment shows the subject to still have either a CR or CRi then the CR or CRi can still be considered. Any completed disease assessment following 2 or more consecutively missed disease assessments will not be considered.

Proportions will be presented as percentages with frequency counts together with the Clopper-Pearson 95% CI.

10.2.5. Transplantation Rate

The proportion of subjects undergoing a HSCT after treatment start during the conduct of this study will be calculated over the total number of subjects in the ITT population. Proportions shall also be calculated based on whether the transplantation is the first, second, or subsequent transplants post PI administration.

Proportions will be presented as percentages with frequency counts together with the corresponding Clopper-Pearson 95% CI. Collected data will be also listed.

10.2.6. Subject/blast Characteristics Correlating with Response

Laboratory results obtained at baseline/screening [peripheral white blood cell (WBC) and blast count, bone marrow blast percentage, cytogenetics, molecular alterations, etc.] will be evaluated in association with response parameters by means of correlation. Response will be categorized in two levels (response and non-response), as done for the primary efficacy endpoint analysis and for ORR analysis.

The following parameters will be analyzed:

- Hematology
  - WBC count
  - Absolute blasts
  - Absolute neutrophils
  - Platelets
- Peripheral blood smear blasts
- Bone Marrow differential
- Cytogenetics (Karyotype Description)
  - t(8;21)
  - inv(16)
  - Normal
  - +8
  - t (9;11)
  - complex (>/= 3 abnormalities)
  - -5
  - -7
  - 5q-
  - 7q-
  - 11q 23 abnormalities
  - inv (3)
  - t (3;3)
  - t (6;9)
  - Other
- Cytogenetics (Gene mutations)
  - FLT3-ITD
  - FLT3-TKD
  - NPM
  - CEBPA
  - MLL
  - WT
  - NRAS
  - None

Point-biserial correlation coefficient will be computed for continuous parameters, while rank point-biserial correlation coefficient will be computed for parameters expressed as ordinal categories (e.g. megakaryocytes and cellularity). Phi coefficient will be computed for parameters expressed as nominal dichotomous categories.

Summary statistics and listings will be provided for cytogenetics.

11. SAFETY ANALYSES

The purpose of this section is to describe the safety analyses for the treatment period of the study (after signing ICF/IAF and until the 28-day safety follow-up visit). For subjects who will enter the OEP, AEs will be reported for the two treatment periods, the fixed and the OEP period, the latter including the 28-day safety follow-up visit.

Drug-related SAEs will be collected and reported for the whole period of the study, i.e. including the 5 year follow-up period.

Listing for safety analyses will be provided for safety population if not otherwise specified.

11.1. Adverse Events

Adverse Events will be coded according to MedDRA dictionary version18.0 or higher. The severity of AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) (version 4.03, May 2009), except for tumor flare reaction, which is defined using CTCAE version 3.

All AEs will be recorded by the Investigator from the time the subject signs the ICF/IAF until 28 days after the last dose of lenalidomide and those SAEs made known to the Investigator at any time thereafter that are suspected of being related to lenalidomide.

In the occurrence of partial dates, refer to Appendix 18.4 where date the imputation guideline is located.

Treatment-emergent adverse events (TEAEs) are defined as any AE occurring or worsening on or after the first treatment of the IP and within 28 days after the last dose administration date. All TEAEs, AEs leading to IP discontinuation, AEs leading to dose reduction/ interruption, AEs related to lenalidomide, and SAEs and AEs leading to death will be summarized by cycle up to a 28-day period after last cycle (see section 5.2), as well as by subject worst recorded grade per event type, SOC, PT and grade. A summary of AEs with NCI CTCAE v 4.0 Grade 3 or higher (except for tumor flare reaction, which is defined using CTCAE version 3), as well as the most frequent PTs, will also be provided by grade and PT. If a subject experiences the same AE more than once with different severity grade, then the event with the highest grade will be tabulated in "by grade" tables. If a subject experiences multiple AEs under the same PT/SOC, then the subject will be counted only once for that PT/SOC. In addition, AEs with a missing intensity will be presented in the summary table as an intensity category of "Missing".

11.1.1. Overview of TEAEs

The number and percentage of subjects experiencing TEAEs will be summarized in the following categories:

- All TEAE
- All TEAE related to lenalidomide;
- NCI CTC grade 3/4 TEAE;
- Treatment related NCI CTC grade 3/4 TEAE;

- NCI CTC grade 5 TEAE;
- Serious TEAE;
- Treatment-related serious TEAE;
- Serious TEAE leading to dose discontinuation;
- TEAE leading to dose discontinuation;
- TEAE leading to dose reduction;
- TEAE leading to dose interruption;
- TEAE leading to death.

11.1.2. TEAEs by System Organ Class and Preferred Term

The incidence of TEAEs will be summarized by MedDRA SOC and PT. The intensity of AEs will be graded 1 to 5 according to the NCI CTCAE.

Tables summarizing the incidence of TEAEs will be generated for each of the following:

- All TEAEs;
- All TEAEs with CTCAE grades 3 or 4;
- All TEAE by CTCAE grade;
- TEAEs reported as treatment-related;
- Treatment-related CTCAE grade 3 or 4 TEAEs;
- Treatment-related CTCAE grade 3 or 4 TEAEs by CTCAE grade;
- CTCAE grade 5 TEAEs;
- Serious TEAE;
- TEAEs leading to death
- Treatment-related serious TEAEs;
- Serious TEAEs leading to discontinuation of lenalidomide
- TEAEs leading to discontinuation of lenalidomide
- TEAEs leading to dose reduction;
- TEAEs leading to dose interruption;
- TEAEs by cycle;
- TEAEs with CTCAE grade 3 or 4 by cycle;
- Non-treatment emergent AEs.

Frequency distributions for shift from baseline to the maximum CTCAE grade during treatment period will be presented for all grades and focusing on grade 3 or 4.

System organ classes are sorted by descending order of frequency of SOC, and by descending order of frequency of PT within SOC, according to the overall column. In tables where the two treatment periods and the overall period are reported, the sorting order will be defined on the basis of frequencies found in the overall column.

For all tables showing results by cycle, OEP and 12th cycle will be considered as a unique cycle labelled "Cycle 12 and higher".

Listing of AE, SAE, SAE of special interest and AE leading to treatment discontinuation will be provided in separated displays.

11.1.3. Adverse Events of Special Interest

Selected TEAEs/ serious AEs (SAEs) of interest, including second malignancies and cardiovascular events, as determined by the mechanism of action, known class effects, or TEAEs observed to date will be summarized. Standardized MedDRA queries (SMQs) will be used in the search strategy for some of the selected AEs of special interest related to study drug, intending to aid in case identification. The groupings of selected AEs, described by one phrase or topic term will be determined by clinicians based on SMQ or relevant search terms and provided to statistician, prior to database lock.

Analysis of AEs of special interest will be presented with tabulations for: summary of TEAEs of interest by category, TEAEs of interest, NCI-CTCAE grade 3 or 4 TEAEs of interest, TEAEs of interest related to study medication, NCI-CTCAE grade 3 or 4 TEAEs of interest related to study medication, serious TEAEs of interest, serious TEAEs of interest related to study medication, serious TEAEs of interest and TEAEs of interest leading to study medication discontinuation, TEAEs of interest by CTCAE maximum grade 1 or 2 and 3 or 4 and TEAEs of interest by CTCAE maximum grade. The following AE of interest categories and preferred terms include but are not limited to:

- Thrombocytopenia and bleeding
- Neutropenia and infection
- Venous thromboembolism
- Cutaneous reactions
- Hypersensitivity and angioedema
- Diarrhoea and constipation
- Peripheral neuropathy
- Cardiac failure and cardiac arrhythmia
- Renal failure
- Ischaemic heart disease (previously myocardial infarction)
- Interstitial lung disease (interstitial pneumonitis)
- Liver function laboratory abnormalities
- Second primary malignancies (SPMs)

- Tumor lysis syndrome (TLS)
- Tumor flare reaction (TFR)
- Graft versus host disease (GVHD)

Frequency distributions for shift from baseline to the maximum CTCAE grade during treatment period will be presented for all grades and focusing on grade 3 or 4.

All AEs of special Interest will be identified by appropriate MedDRA preferred term.

11.2. Deaths

Deaths during treatment (defined as deaths from the day of first dosing to 28 days after the last dose of study medication) and during the follow-up will be summarized by frequency of occurrence and corresponding percentage by cause of death per period (during treatment or follow-up) as well as overall. Listings of all deaths will be provided.

11.3. Second Primary Malignancy

Second primary malignancies are any occurring regardless of relationship to study drug during the conduct of the study including up to 5 years after last subject first dose date.

Events of SPMs will be tabulated for the following categories:

- All SPMs (invasive and non-invasive SPMs)
- All invasive SPMs (hematologic and solid tumor SPMs)
- All hematologic SPMs (AML, myelodysplastic syndromes (MDS), MDS to AML (for MDS events that transform to AML), B-cell malignancies, and other hematologic cancers)
- All solid tumor SPMs
- All non-invasive SPMs (non-melanoma skin cancers)

For each of the above SPM categories, SPMs will be further tabulated using the MedDRA preferred term. Each subject is counted only once within each SPM category as well as within each preferred term.

Additionally, the number and percentage of subjects with SPMs who died and those who did not die will be tabulated by SPM category.

It should be noted that these analyses with regard to SPMs are based on the number of subjects with at least one SPM and not the total number of SPMs.

For each SPM category, time to onset will be calculated as time (in months) from the start of the study treatment to the onset of the SPM for each affected subject. For the subjects with more than one new malignancy within an SPM category, the onset of the earliest SPM will be used. Time to onset will be summarized descriptively for each SPM category [mean, median, Standard Deviation (StdDev), first quartile (Q1), third quartile (Q3), minimum (Min), and maximum (Max)].

A scatter plot to graphically display the time to onset of hematologic and solid tumor SPMs for each SPM by dose level will be provided.

For each SPM category, the incidence rate per 100 person-years will be calculated as: (the number of subjects with any SPM in the SPM category/total person-years)*100. Total person-years are defined as the total time from the date of first treatment to the first onset date of the specified SPM for subjects with the specified SPM plus the total time from the date of first treatment to the date of the last follow-up or death for subjects without the specified SPM. Incidence rates per 100 person-years and the 95% confidence intervals will be calculated for each treatment arm and SPM category. Confidence interval at 95% level for the incidence rate per 100 person-years is calculated as follows: incidence rate*exp{+/-1.96*n^(-1/2)}.

Listings for "Second Primary Malignancies" and for "Second Primary Malignancies Procedures for Cancers Not Under Study" will be produced by Celgene.

11.4. Clinical Laboratory Evaluations

Clinical laboratory values from the local laboratories will be graded according to NCI CTCAE version 4.03 for applicable tests using computerized programs. Frequency distributions for shift from baseline to the worst grade during treatment period will be presented.

Local lab results will be converted to standard units by a programmer using standard conversion factors and then each standardized result will be compared to literature reference ranges according to the age of the subject in order to compute the abnormality flags. Laboratory normal ranges from literature were provided by the Sponsor and can be found in Section 18.5.

Listings of clinical laboratory data from local laboratory with abnormal flags (H=High, L=Low) will be provided by subject and by parameter.

Both original and standardized results will be listed.

11.4.1. Hematology

Hematology testing including red blood cell (RBC) count, hemoglobin, hematocrit, mean corpuscular volume (MCV), WBC count and manual differential count (including blasts %, immature myeloid, absolute monocyte count, absolute neutrophil count (ANC)), and platelet count will be evaluated by the local laboratory at screening, on Days 1, 8, 15, and 22 of Cycles 1 and 2, on Day 1 of every cycle thereafter, at the Treatment Discontinuation Visit, on the 28-day Follow-up Visit, and at unscheduled visits.

White blood cell count, absolute blasts, absolute neutrophils and platelets will be recorded in the eCRF and results for all other hematology laboratory assay will not be collected on the eCRF but, instead, laboratory abnormalities that are considered AEs will be reported as AEs on the AE eCRF page.

The number and percentage of subjects with each NCI CTCAE grade will be presented for the parameters where grade will be assigned using computerized programs. A shift table representing the shift from the baseline grade to the worst grade (i.e. any time after first dose of study drug) will be provided for the safety population.

All collected hematology parameters will be presented in a listing for the ITT population.

11.4.2. Chemistry Laboratory Assessments

Serum chemistries including sodium, potassium, chloride, bicarbonate, calcium, phosphorus, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH), and uric acid will be evaluated by the local laboratory at screening, on Days 1, 2, 4, 8, 15, and 22 of Cycle 1, on Days 1, 8, 15, and 22 of Cycle 2, on Day 1 of every cycle thereafter, at the Treatment Discontinuation Visit, on the 28-day Follow-up Visit, and at unscheduled visits. Serum chemistry laboratory values will not be collected on a laboratory eCRF; instead, laboratory abnormalities that are considered AEs should be reported on the AE eCRF page. No descriptive analysis of the chemistry laboratory results will thus be provided.

11.4.3. Urinalysis (dipstick)

No report will be provided for urinalysis.

11.5. Vital Signs

Vital signs (including sitting blood pressure, heart rate, respiration, and temperature) will be measured at screening, on Days 1, 8, 15, and 22 of Cycle 1, bi-weekly during Cycle 2, on Day 1 of every cycle thereafter, at the Treatment Discontinuation Visit, on the 28-day Follow-up Visit. At unscheduled visits vital signs will be measured. Height will be collected only at screening and on Cycle 1 Day 1. However, weight will be collected at screening and Day 1 of every cycle for dose adjustment.

Baseline is defined as the latest value collected on or before the date when the first dose of study treatment is administered. If multiple values are present for the same date, the mean of these values will be used as the baseline.

Summary statistics (n, mean, median, StdDev, Q1, Q3, Min, and (Max) of observed and change from baseline values will be presented.

Shift from baseline to worst value during the treatment (most extreme post-baseline value, where most extreme includes low and high category) will be displayed in cross–tabulations. For each vital sign parameter, the baseline grade and the worst grade post-baseline will be determined for each subject classified in below, within, and above the normal ranges. This table may include subjects with both normal and missing results for the vital sign, provided no abnormal (low or high) results will be reported. Low and high categories will be presented separately. In Table 3 normal ranges are reported.

Table 3 Normal Ranges of Vital Sign Measurements

Test	Age group[1]	Normal Range (Unit)
Diastolic Blood Pressure (DBP)	<2	[34,66] (mmHg)
	2-5	[34,74] (mmHg)

Test	Age group[1]	Normal Range (Unit)
	6-8	[35,80] (mmHg)
	9-13	[37,87] (mmHg)
	14-16	[40,91] (mmHg)
	≥17	[40,89] (mmHg)
Systolic Blood Pressure (SBP)	<2	[58,112] (mmHg)
	2-5	[60,125] (mmHg)
	6-8	[65,131] (mmHg)
	9-13	[68,141] (mmHg)
	14-16	[76,153] (mmHg)
	≥17	[70,139] (mmHg)
Pulse Rate	1-2	[95, 178] (bpm)
	3-7	[62, 124] (bpm)
	8-15	[48, 110] (bpm)
	≥16	[60, 100] (bpm)
Temperature	All	[35, 38] (°C) [95, 100.4.] (F)
Respiratory Rate	1-3	[24,50] (BPM)
	4-6	[22,34] (BPM)
	7-12	[18,30] (BPM)
	13-21	[12,16] (BPM)

1- Years reached at the time of the assessment.

Listings will be provided for all vital sign parameters for the ITT population.

11.6. Rates of acute and chronic graft-versus-host disease (GVHD)

Graft-versus-host disease (GVHD) will be summarized as collected in the "Adverse Events" eCRF page with the following preferred terms: "Acute graft versus host disease", "Chronic graft versus host disease" and "Overlap syndrome".

The incidence of GVHD TEAEs will be summarized by maximum CTCAE grade (1 or 2, higher than 2) within type of GVHD (overall, overlap, acute, chronic and overlap + acute GVHD).

Safety population subjects that had previous transplant (as collected in the "Stem Cell Transplants" eCRF page) will be selected for these summary tables and their total number will be used as denominator for the computation of incidence rates.

GVHD data as collected in the "GVHD" eCRF page will also be listed.

11.7. Karnofsky or Lansky Performance Status Score

Performance status will be measured using either the Karnofsky or Lansky performance status score (Karnofsky performance status score for subjects ≥ 16 years of age or Lansky performance status score for subjects < 16 years of age) at screening, on Day 1 of each cycle and at the Treatment Discontinuation Visit. For performance status scores, shift from baseline to worst value and best score during the treatment period will be displayed for the whole treatment period and by cycle. Subjects changing age category during the study, ie, having both performance status results, will be included into the summary statistics computation.

Performance status scores will also be presented in a listing for the ITT population.

11.8. Other Safety Assessments

Data collected for other safety assessments including pregnancy status, chest x-ray, electrocardiogram and echocardiography will be listed.

Summary of pregnancy status will be provided for females of childbearing potential.

13. PHARMACOKINETIC (PK) ANALYSES

13.1. Pharmacokinetics

13.1.1. Handling of Pharmacokinetic Data

Concentrations that are below the limit of quantitation (BLQ) prior to the first dose will be assigned a numerical value of zero. Post-treatment concentrations that are BLQ will be treated as missing. Concentrations assigned a value of missing will be omitted from the descriptive statistics. A concentration value of zero will be excluded from the computation of the geometric mean (geometric CV%). Geometric CV(%) is calculated as follows: CV (%)=100× SQRT(exp(V)-1), where V denotes the variance of the log-transformed values.

If any subjects are found to be noncompliant with respect to dosing, have incomplete data, or encounter other circumstances that would affect the evaluation of pharmacokinetics, a decision will be made on a case-by-case basis as to their inclusion in the PK analysis. Data excluded from pharmacokinetic analysis will be included in the data listings, but not in the summaries.

In tables and listings for the derived PK data, there should be four decimal places for numerical values below 1, three decimal places for numeric values below 10 but above 1, and two decimal places for numeric values above 10. However, the listings of raw data should not have more or fewer decimal places than the actual data.

13.1.2. Pharmacokinetic Parameters

Pharmacokinetic parameters of lenalidomide will be calculated from concentration-time profiles using non-compartmental methods, though compartmental analysis may be employed if appropriate. Pharmacokinetic parameters will include, but not be limited to:

- C_{max}: observed maximum plasma concentration
- T_{max}: observed time to maximum plasma concentration
- AUC_t: area under the plasma concentration-time curve from time zero to the last quantifiable timepoint, calculated by the linear trapezoidal rule
- AUC_{24}: area under the plasma concentration-time curve from time zero to 24 hours postdose calculated by the linear trapezoidal rule
- AUC_∞: area under the plasma concentration-time curve from time zero to infinity, calculated by the linear trapezoidal rule and extrapolated to infinity will be calculated according to the following equation:
  $AUC_\infty = AUC_t + (C_t/\lambda z)$, where C_t is the last quantifiable concentration.
- λz: terminal phase rate constant, determined by linear regression of the terminal points of the log-linear plasma concentration-time curve. Visual assessment may be used to identify the terminal linear phase of the log concentration-time profile. A minimum of 3 data points will be used for the calculation. The λz will not be

estimated if the terminal phase of the log-concentration-time profile does not exhibit a linear decline phase, or if the regression coefficient (Rsq) is less than 0.8

- $t_{½}$: terminal phase half-life, calculated as $t_{½} = [0.693/\lambda z]$
- CL/F: apparent total clearance when dosed orally, calculated as $[Dose/AUC_{\infty}]$
- Vz/F: apparent volume of distribution when dosed orally, calculated as: $Vz = [CL/\lambda z]$

The following plasma PK parameters will be calculated for diagnostic purposes summarized and listed,.

- λ_z lower: lower limit of time (h) included in the calculation of λ_z
- λ_z upper: upper limit of time (h) included in the calculation of λ_z
- λ_z N: number of data points used in the calculation of λ_z
- Rsq: regression coefficient for calculation of λz
- AUC %extrap: percentage of $AUC\infty$ due to extrapolation from the time for the last quantifiable concentration to infinity, calculated as $(AUC\infty\text{-}AUCt)/AUC\infty*100$

The PK parameters shown above will be calculated from samples collected on Day 1 as described in section 18.2.1. Additional parameters may also be calculated. Actual blood draw times relative to dosing will be used for all plasma PK parameters computations.

Only subjects included in the PK population shall be considered for PK analysis.

13.1.3. Presentation of Pharmacokinetic Results

Listings of PK blood sample collection times, derived sampling time deviations, drug concentrations, and PK parameters will be provided by subject in the PK population.

Plasma concentrations for lenalidomide will be summarized by nominal time points or collection intervals, including sample size (N), mean, StdDev, % coefficient of variation (CV%), geometric mean, geometric CV%, minimum, median, and maximum. Mean (±StdDev) and

individual plot of lenalidomide plasma concentrations versus time will be presented in both linear scale and semi-logarithmic scale.

PK parameters will be summarized descriptively (N, mean, StdDev, CV%, geometric mean, geometric CV%, minimum, median, and maximum) by age class (1 to < 6, 6 to < 12 and >=12 years) and overall.

13.1.4. Population Pharmacokinetic Analysis

Lenalidomide concentration data from this study will be combined with the concentration data from other pediatric studies and literature data to perform a population pharmacokinetic analysis. Main pharmacokinetic parameters in plasma to be estimated include AUC, C_{max}, apparent clearance, and apparent volume of distribution. Effect of age and body size on lenalidomide PK will be assessed. Other relevant covariates for the main PK parameters may be identified. The between-subject variability for PK parameters will be estimated. If data allow, main PK parameters (clearance and volume of distribution) will be summarized by age as appropriate (eg, 1 to < 6, 6 to < 12, and >=12 years).

This analysis is not within the scope of this SAP and report, as it will be documented in a separate report.

14. INTERIM ANALYSIS

Periodic reports (at least semi-annually) will be provided to an external data monitoring committee (DMC). The first DMC meeting will be held after 4 subjects have completed at least 1 cycle of study treatment, if having not stopped therapy earlier due to a safety issue, in order to evaluate safety and provide a recommendation.
An interim analysis is planned to take place, at the end of Stage 1, once the first 18 subjects evaluable for the primary endpoint have been accrued and completed up to 4 cycles of lenalidomide treatment if they have not stopped therapy before 4 cycles, ie, the RR population. The interim analysis will assess the number of subjects with CR or CRi under lenalidomide treatment. If fewer than 3 of 18 subjects achieve a response then the study will be closed; otherwise the study shall continue as planned and enrollment shall continue into Stage 2.

At the interim analysis, only a subset of the summary outputs detailed in this SAP will be produced. No figures and listings will be provided, with the exception of AE listings. These summaries will include: analysis populations, subject disposition, demography and baseline characteristics, concomitant medications and procedures, morphological complete response rate within the first four cycles of treatment, overall response rate, summary of disease assessment outcome, summaries on exposure to lenalidomide, TEAE, TEAE with CTCAE grades 3 or 4, TEAE with CTCAE grade 3 or 4 related to lenalidomide, TEAE with CTCAE grade 5, cause of death during treatment period and cause of death after 28 days of end of treatment.

Should the study stop after Stage 1 then the primary final analysis will take place.

15. PRIMARY AND END OF STUDY FINAL ANALYSES

All tables, listings and figures detailed in this SAP will be provided for the primary final analysis that will be conducted when all on treatment subjects will have completed their Cycle 4 Day 28 assessments or will have met discontinuation criteria, whichever occurs first.

For the end of study final analysis, all outputs will be rerun once all subjects will have discontinued the follow-up period (up to 5 years after the last subject first dose of lenalidomide).

16. Changes to the Statistical Analyses Section of the Protocol

Denominator of the ORR rate will be defined as the number of subjects starting the cycle of interest instead of the number of subjects completing the cycle of interest as stated in the protocol.

Correlation will be computed between response and laboratory results obtained at baseline, instead of correlation between response and laboratory results at diagnosis and relapse as stated in the protocol.

The IWG response criteria in this study was brought in line with the actual criteria, ie. 'Progressive Disease' was replaced with 'Treatment Failure'.

Time to response endpoint was added as a secondary endpoint.

During the course of the study, due to a low (1 or fewer) number of subjects reporting certain measurements or to redundant presentation, it was determined that the analyses listed below would not be conducted:

- Summaries of prior cancer history, prior procedures/surgeries, procedures for prior cancers not under study and radiation treatment for prior cancers not under study.
-
- Correlation between response with baseline/screening peripheral white blood cell count, absolute blast count, cytogenetics,
- Summary of durable response rate.
- AE summary tables for (treatment-emergent adverse events leading to death, SAEs related to lenalidomide, SAEs leading to discontinuation, Grade ¾ TEAEs by maximum intensity.
- Summary for AE of special interest related to lenalidomide, SAEs of special interest related to lenalidomide or leading to discontinuation of lenalidomide. AEs of special interest by maximum intensity.
- Second primary malignancy related tables, listings and figures.
-
- Population PK analysis.

17. REFERENCES

Cheson B, Bennett J, Kopecky K, Buchner T, Willman CL, Estey EH, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol 2003;21(24):4642-4649.

18. APPENDICES

18.1. Modified International Working Group AML Response Criteria

Hematologic Response According to IWG Criteria for AML is reported in table Table 4.

Table 4: Hematologic Response According to IWG Criteria for AML

Category	Definition
Morphologic Complete Remission (CR)	The following conditions should be met: • Absolute neutrophil count (ANC) > 1000/uL and platelets > 100,000/uL without transfusions and/or exogenous growth factor support (ie, no transfusion or exogenous growth factor within 7 days of assessment). • Bone marrow with < 5% blasts and evidence of trilineage hematopoiesis. • No evidence of extramedullary disease.
Morphologic Complete Remission With Incomplete Blood Count Recovery (CRi)	• ANC < 1000/uL. • Platelets < 100,000/uL or > 100,000/uL without platelet recovery (requiring transfusion within 7 days of assessment). • Bone marrow with < 5% blasts and evidence of trilineage hematopoiesis. • No evidence of extramedullary disease.
Partial Remission (PR)[a]	• ANC > 1000/uL and platelets > 100,000/uL without transfusions and/or exogenous growth factor support (ie, no transfusion or exogenous growth factor within 7 days of assessment). • Bone marrow with 5% to 25% blasts and at least a 50% decrease in bone marrow blast percent from baseline. • No evidence of extramedullary disease.
Treatment Failure	Resistant Disease: Patient survives ≥ 7 days post-therapy and failed to achieve CR, CRi, or PR but are stable with persistent AML in blood or bone marrow.

Category	Definition
	Aplasia: Patient survives ≥ 7 days post-therapy; death while cytopenic, with aplastic bone marrow. Indeterminate cause: • Patients who die < 7 days post-therapy. • Patients who die > 7 days post-therapy with no peripheral blood blasts, but no bone marrow examination. • Patients who do not complete the first course of therapy. Morphologic relapse after CR or CRi: • the reappearance of > 5% blasts in the peripheral blood, or • a single finding of > 15% blasts in the bone marrow. All of the above occurrences should be attributed to relapse following CR or CRi and not attributable to another cause (eg, bone marrow regeneration after consolidation therapy). Molecular or cytogenetic relapse: Reappearance of molecular or cytogenetic abnormality.

[a] If the pretreatment bone marrow blast percentage was 50% to 100%, the percentage of blasts must decrease to a value between 5% and 25%; if the pretreatment blast percentage was 20% to less than 49%, they must decrease by at least half to a value of more than 5%.

Source: Cheson, 2003.

18.2. Pharmacokinetic Sample Collection

18.2.1. Blood Collection for PK Analysis

Collection of blood samples for PK assessments in plasma will be performed in all subjects. On Cycle 1 Day 1, the subjects will receive the dose of lenalidomide in the morning at the study center. Subjects will undergo PK sampling of blood at scheduled time points (Table 5) for 24 hours post-dose. The actual date and time for dosing and blood sampling should be recorded in the eCRF.

Table 5: PK Sampling Schedule During Cycle 1 Day 1

Collection time after lenalidomide administration[a]	Collection window	Weight ≤ 20 kg[b]	Weight > 20 kg[c]
0.5 hour	± 10 min	-	x
1 hour	± 10 min	x	x
2 hours	± 10 min	x	x
4 hours	± 10 min	x	x
6 hours	± 10 min	-	x
8 hours	± 10 min	x	x
24 hours*	± 2 hours	x	x

PK = pharmacokinetic.
* The 24 hour blood sample must be taken prior to the lenalidomide administration on Day 2.
[a] The blood draw volume is 1 mL per sample.
[b] Only 5 PK blood samples will be taken from subjects with weight ≤ 20 kg at the specified time points.
[c] Seven PK blood samples will be taken from subjects with weight > 20 kg.

18.3. Handling of Dates

Dates will be stored as numeric variables in the SAS analysis files and reported in DDMMMYYYY format (i.e., the Date9. date format in SAS). Dates in the clinical database are classified into the categories of procedure dates, log dates, milestone dates, outcome dates, and special dates.

- **Procedure Dates** are the dates on which given protocol-specified procedure are performed. They include the dates of laboratory testing, physical examinations, tumor scans, etc. They should be present whenever data for a protocol-specified procedure are present and should only be missing when a procedure are marked as NOT DONE in the database. Procedure dates will not be imputed.
- **Log Dates** are dates recorded in eCRF data logs. Specifically, they are the start and end dates for adverse events and concomitant medications/procedures. They should not be missing unless an event or medication is marked as *ongoing* in the database. In listings, log dates will be shown as recorded without imputation.
- **Milestone Dates** are dates of protocol milestones such as randomization, study drug start date, study drug termination date, study closure date, etc. They should not be missing if the milestone occurs for a subject. They will not be imputed.
- **Outcome Dates** are dates corresponding to study endpoints such as survival, treatment failure, etc. In most cases they are derived either from a milestone (eg, the survival date is derived from the death date), or a procedure date (eg, the treatment failure date is derived from the date of the tumor scan that was used to determine treatment failure). They may be subject to endpoint-specific censoring rules if the outcome did not occur, but are not otherwise subject to imputation.
- **Special Dates** cannot be classified in any of the above categories and they include the date of birth. They may be subject to variable-specific censoring and imputation rules.
- **Last Contact Dates** for the survival analysis are the maximum date collected in the database. If the imputed date used for response date or AE date, the last contact dates should be the latest date of those imputed date and maximum date in the database.

Dates recorded in comment fields will not be imputed or reported in any specific format.

18.3.1. Calculation Using Dates

Calculations using dates (e.g. subject's age or relative day after the first dose of study drug) will adhere to the following conventions:

- Study days after the start day of study drug will be calculated as the difference between the date of interest and the first date of dosing of study drug plus 1 day. The generalized calculation algorithm for relative day is the following:
  - If TARGET DATE >= DSTART then STUDY DAY = (TARGET DATE – DSTART) + 1;
  - Else use STUDY DAY = TARGET DATE – DSTART.

Note that Study Day 1 is the first day of treatment of study drug. Negative study days are reflective of observations obtained during the baseline/screening period. Note: Partial dates for the first study drug are not imputed in general. All effort should be made to avoid incomplete study drug start dates.

- Age (expressed in days) is calculated: AGE = CONSENT DATE – DATE of BIRTH + 1. In practice, age will be transformed to years by dividing the difference by 365.25 days, then truncating.
  - Preference is for using calculated age from clinical database. When not available, calculated age from eCRF or IVRS may be used
  - Partial birth date: impute missing day as 1st of the month; set missing age for missing month; set missing age for missing year
- Age in listings will be displayed in years and months and will be calculated as follows:
  - first, the age in months will be calculated as:
    Integer part of [age expressed in days / 30.4375]
  - then, the resulting number will be divided by 12 in order to express age in years and months:
    integer part of [(age in months / 12)] years and [remainder of (age in months / 12)] months
- Intervals that are presented in weeks will be transformed from days to weeks by using (without truncation) the following conversion formula:

  WEEKS = DAYS /7
- Intervals that are presented in months will be transformed from days to months by using (without truncation) the following conversion formula:

  MONTHS = DAYS /30.4375

18.4. Date Imputation Guideline

18.4.1. Impute Missing Dates for Adverse Events/ Prior or Concomitant Medications

Incomplete Start Date

- If the stop date is not missing, and the imputed start date is after the stop date, the start date will be imputed by the stop date.

Missing day and month

- If the year is the **same** as the year of the first dosing date, then the day and month of the first dosing date will be assigned to the missing fields.
- If the year is **prior to** the year of first dosing date, then December 31 will be assigned to the missing fields.

- If the year is **after** the year of first dosing, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year are the **same** as the year and month of first dosing date, then the first doing date will be assigned to the missing day.
- If either the year of the partial date is **before** the year of the first dosing date or the years of the partial date and the first dosing date are the same but the month of partial date is **before** the month of the first dosing date, then the last day of the month will be assigned to the missing day.
- If either the year of the partial date is **after** the year of the first dosing date or the years of the partial date and the first dose date are the same but the month of partial date is **after** the month of the first dosing date, then the first day of the month will be assigned to the missing day.

Missing day, month, and year

- No imputation is needed, the corresponding AE will be included as TEAE if end date of AE is after the first dose date or the end date is also missing.

Incomplete Stop Date

- If the imputed stop date is before the start date, then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the **same** as the year of the last dosing date, then the day and month of the last dosing date will be assigned to the missing fields.
- If the year of study drug start and stop are different, and the year of the incomplete stop date is the **same** as the year of the first dosing date, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date but is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing date.
- If the year of the incomplete stop date is **after** the year of the last dosing date, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year of the incomplete stop date are the **same** as the month and year of the last dosing date, then the day of the last dosing date will be assigned to the missing day.
- If either the year of the partial date is **not equal to** the year of the last dosing date or the years of the partial date and the last dosing date are the same but the month of

partial date is **not equal to** the month of the last dosing date, then the last day of the month will be assigned to the missing day.

18.4.1.1. Adverse Events

Partially missing AE start dates will be imputed in the derived dataset for AEs, but partially missing AE end dates will not be imputed in the same dataset. If the AE end date is complete with no missing year, month, or day, and the partially missing start date imputed by the rules below is after the AE end date, then the start date will be imputed by the AE end date.

18.4.1.2. Prior/Concomitant Medications/Procedures

Partially missing start/stop dates for prior/concomitant medications and partially missing start dates for prior/concomitant procedures will be imputed in the derived dataset for prior/concomitant medications/procedures. For prior/concomitant medications, if the stop date is complete with no missing year, month, or day, and the partially missing start date imputed by the rule below is after the stop date, then the start date will be imputed by the stop date.

Partially missing prior/concomitant medication/procedure start dates will be imputed by the earliest possible date given the non-missing field(s) of the date.

Partially missing prior/concomitant medication stop dates will be imputed by the latest possible date given the non-missing field(s) of the date.

18.4.2. Medical History

Partially missing medical history start dates will be imputed in the derived dataset for medical history. The 16th of the month will be used to impute a partially missing start date that has only the day missing, and July 1st will be used to impute a partially missing start date that has both the month and day missing.

18.5. Reference Ranges from Literature

Table 6 Laboratory Reference Ranges from Literature

TEST NAME	Gender (F,M or Both)	AGE For non-specific age range enter 0-99		RANGE		UNITS
		LOW (>/=)	HIGH (<)	LOW	HIGH	
White blood cell count (WBC) (B)	Both	1–6yrs		5.0–14.5		$10^3/\mu L$
		7–12yrs		5.0–14.5		
		13–18yrs		4.5–13.5		
		≥19yrs		4.5–11.0		
Absolute Neutrophil Count (ANC) (B)	Both	1–6yrs		1.5–8.0		$10^3/\mu L$
		7–12yrs		1.5–8.0		
		13–18yrs		1.8–8.0		
		≥19yrs		1.8–7.7		
Platelet count (B)	Both	0-99		150,000–450,000		µL