DISCLOSURE

REDACTED PROTOCOL AMENDMENT 2

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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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

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

Study Title

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.

Indication: Treatment of pediatric subjects (from 1 to ≤ 18 years of age) with second or greater relapse or refractory acute myeloid leukemia (rrAML).

Objectives

Primary

- To determine the activity of lenalidomide in the treatment of pediatric subjects with relapsed/refractory acute myeloid leukemia (AML) (with second or greater relapse or refractory to at least 2 prior induction attempts) measured by morphological complete response defined as either a complete response (CR) or complete remission with incomplete blood count recovery (CRi) within the first 4 cycles of treatment.

Secondary

- 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, duration of response (DoR) 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.

Study Design

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 70 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 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 AML to warrant subsequent study.

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

The Optional Extension Phase 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 second primary malignancies (SPMs) will be monitored (Table 2).

An external data monitoring committee (DMC) will evaluate safety and treatment activity 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. Once 4 subjects having received at least one dose of lenalidomide have completed at least 1 cycle of study treatment or discontinued treatment (whichever occurs first), the DMC will evaluate the safety data available 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 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.

As part of the screening procedures, a fresh bone marrow aspirate (BMA) and/or a bone marrow biopsy paraffin embedded slide will be collected from all subjects for confirmation of disease. The confirmation of disease will be performed locally.

A standard cytogenetic metaphase preparation from the fresh BMA must be prepared for the cytogenetic testing/chromosome analysis including karyotype. The local site will submit the reports of the karyotype, fluorescent in situ hybridization (FISH) studies, as well as any available data on molecular mutations (FLT3, CEPBa, NPM1, and others including exome sequencing via Foundation Medicine or other sources) if performed, to the central reviewer at the . If subjects have a FISH detectable marker, the test should be repeated until CR/CRi and at relapse.

The BMA slide (and/or bone marrow biopsy paraffin embedded slide) and peripheral blood smear from screening **must** be provided to the central reviewers at . The central review will provide standardized analysis and reporting for all subjects. The central reviewer's assessment will be used retrospectively to confirm diagnosis.

Creatinine clearance (CLcr) will be measured at screening using Table 4 (see Section 7.2).

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 as per the Investigator may continue to receive lenalidomide in an OEP (Appendix L) 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 (Table 6). 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. For additional details regarding dose reductions and dose capping see Section 8.2.1.

During the Treatment Phase, subjects will be assessed for treatment activity based on modified IWG AML Response Criteria (Appendix D). To determine morphologic CR/CRi, BMA/biopsy and peripheral blood smear must be collected from all subjects at the completion of the 21-day treatment period of the predefined treatment Cycles 1, 2, 3 and 4 within 6 days **before dosing for each subsequent cycle** (ie, between Day 22 to Day 27 of that cycle) (Table 2). If morphologic CR/CRi is achieved within the first 2 cycles, BMA/biopsy and peripheral blood smear will not be required at the end of Cycle 3. For all subjects, BMA/biopsy and peripheral blood smear must be performed at the completion of Cycle 4, and at the Treatment Discontinuation Visit or at the time of suspected relapse (whichever occurs first). For subjects who are assessed as having partial response, the BMA/biopsy and peripheral blood smear will be repeated at Cycle 8 unless the subject goes to allogeneic hematopoietic stem cell transplantation (HSCT), and at the Treatment Discontinuation Visit or at the time of suspected treatment failure

(whichever occurs first). ***A bone marrow biopsy is required only if a bone marrow aspirate cannot be obtained***. Subjects demonstrating clinical benefit as per the Investigator at the end of Cycle 4 and beyond may continue to receive lenalidomide on study for up to 12 cycles in the absence of protocol-defined toxicity or transitioning to allogeneic HSCT.

During the study, repeat of local testing of bone marrow cytogenetics and FISH for any positive markers is to be completed whenever a BMA/biopsy is obtained. However, if the cytogenetics/FISH results are 'normal' at screening or at any point during the study, cytogenetic analysis is not required to be repeated except at the Treatment Discontinuation Visit or at the time of bone marrow evaluation for suspected relapse (whichever occurs first).

In order to establish lenalidomide plasma PK parameters in subjects with rrAML, blood samples will be collected at specified time points (Table 3) for up to 24 hours postdose from all enrolled subjects during Cycle 1 Day 1 (Appendix H).

Dose interruptions, delays and modifications may be required to manage adverse events (AEs) during study treatment (see Section 8.2.1 for details). In order to optimally benefit from protocol-prescribed therapy, the Investigator should aim to treat subjects for **at least 4 cycles** with lenalidomide. Subjects demonstrating clinical benefit as per the Investigator at the end of Cycle 4 and beyond may continue to receive lenalidomide on study up to 12 cycles in the absence of protocol-defined toxicity or transitioning to allogeneic HSCT. Subjects may be treated beyond 12 cycles of study treatment in the OEP if they continue to benefit and have not undergone HSCT.

Subjects may be discontinued from the treatment at the Investigator's discretion for any of the reasons as detailed in Section 12. All discontinued subjects, regardless of reason for discontinuation, should undergo treatment discontinuation procedures at the time of investigational product (IP) discontinuation (Table 2). The reason for discontinuation will be recorded in the electronic case report form (CRF) and in the source document.

Follow-up Phase

Subjects will enter the Follow-up Phase at the time of permanent discontinuation of 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 (see Section 6.8 and Section 7.2).

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 (see Section 12) may enter the optional extension phase.

Details for the OEP are provided in Appendix L.

Study Population

The study population consists of pediatric subjects with rrAML from 1 to ≤ 18 years of age at the time of screening with at least 2 prior induction therapy attempts. Approximately 50% of subjects should be younger than 12 years of age to provide adequate PK data for this age subset.

Length of Study

Enrollment is expected to last approximately 40 months with an accrual rate of 1 to 2 subjects per month. Once 4 subjects having received at least one dose of lenalidomide have completed at least 1 cycle of study treatment or discontinued treatment (whichever occurs first), the DMC will evaluate the safety data available and provide a recommendation. At the end of Stage 1 and following safety and treatment activity data review, the DMC will 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. Subjects demonstrating clinical benefit as per the Investigator at the end of Cycle 4 and beyond may continue to receive lenalidomide on study up to 12 cycles in the absence of protocol-defined toxicity or transitioning to allogeneic HSCT. Once lenalidomide has been discontinued, subjects will be followed up to 5 years from the last subject's first dose, unless consent is withdrawn, the subject is lost to follow-up or dies.

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, or the date of receipt of the last data point from the last subject that is required for primary, secondary analysis, as prespecified in the protocol, whichever is the later date.

Study Treatment

Lenalidomide will be administered either in capsules containing 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg or 25 mg or as an oral suspension (10 mg/mL). The oral suspension is available for use in subjects who are unable to swallow the capsules or at the discretion of the investigator. The

starting dose of lenalidomide will be 2 mg/kg/day with a maximum dose of 70 mg/day. Lenalidomide will be administered orally once daily for the first 21 days of every 28-day cycle.

Daily dosage should be administered using the combinations that yield the least amount of capsules. However, if a subject is unable to swallow big capsules, varying, appropriate strength combinations may be considered during medication assignment using the interactive web response system (IWRS). The prescribed dose should be the closest dose that can be given to the calculated dose based on the strengths of lenalidomide available. For dose reductions, the dose calculated should be to the nearest whole number. For a dosing table with guidelines reflecting this approach for the lenalidomide capsules, refer to Appendix B.

Refer to Appendix C for dosing guidelines for the lenalidomide oral suspension.

Overview of Treatment Activity Assessments

The primary endpoint consists of the assessment of the morphologic complete response, defined as CR or CRi, within the first 4 cycles of study treatment with lenalidomide. These responses will be determined using the modified IWG AML response criteria (Cheson, 2003) (Appendix D).

The morphological complete response rate is defined as the sum of the number of subjects with morphological complete response observed during the first 4 cycles of study treatment divided by the total number of subjects evaluable for the primary endpoint analysis.

During the Treatment Phase, subjects will be assessed for treatment activity based on IWG AML Response Criteria (Appendix D). To determine morphologic CR/CRi, BMA/biopsy and peripheral blood smear must be collected from all subjects at the completion of the 21-day treatment period of the predefined treatment Cycles 1, 2, 3 and 4 within 6 days **before dosing for each subsequent cycle** (ie, between Day 22 to Day 27 of that cycle) (Table 2). If morphologic CR/CRi is achieved within the first 2 cycles, BMA/biopsy and peripheral blood smear will not be required at the end of Cycle 3. For all subjects, BMA/biopsy and peripheral blood smear must be performed at the completion of Cycle 4, and at the Treatment Discontinuation Visit or at the time of suspected relapse (whichever occurs first). For subjects who are assessed as having partial response, the BMA/biopsy and peripheral blood smear will be repeated at Cycle 8 unless the subject goes to allogeneic HSCT, and at the Treatment Discontinuation Visit or at the time of suspected treatment failure (whichever occurs first). ***A bone marrow biopsy is required only if a BMA cannot be obtained.*** Subjects demonstrating clinical benefit as per the Investigator at the end of Cycle 4 and beyond may continue to receive lenalidomide on study for up to 12 cycles in the absence of protocol-defined toxicity or transitioning to allogeneic HSCT.

During the study, repeat of local testing of bone marrow cytogenetics and FISH for any positive markers is to be completed whenever a BMA/biopsy is obtained. However, if the cytogenetics/FISH results are 'normal' at screening or at any point during the study, cytogenetic analysis is not required to be repeated except at the Treatment Discontinuation Visit or at the time of bone marrow evaluation for suspected relapse (whichever occurs first).

In addition, BMA/biopsy will be obtained to confirm CR, CRi, PR, or treatment failure, as assessed by the Investigator based on complete blood count [CBC] with white blood cell (WBC) differential results (defined in Appendix D). Morphological response will be assessed based on

peripheral blood count recovery and morphologic assessment of BMAs/biopsies (Table 2). Assessments to be collected during the Follow-up Phase will include new anticancer therapies, HSCT, SPMs, SAEs,

Overview of Safety Assessments

Subject safety, including hematology (CBC with differential) and serum blood chemistry analyses, physical exams, vital signs, body weight measurement, Lansky/Karnofsky performance status, AEs, concomitant medications/procedures, urinalysis, echocardiograms, electrocardiograms (ECGs), and pregnancy testing for females of childbearing potential/female children of childbearing potential (FCBP/FCCBP) will be assessed as outlined in Table 2. Peripheral blood and bone marrow aspirate/biopsy may be used to assess IP toxicity.

Adverse events will be reported and recorded in the CRF. For SAEs, an expedited reporting procedure will be used (see Section 11). The rate of AEs, SAEs, abnormal laboratory AEs and vital signs (graded according to the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] Version 4.03) will be measured while the subject is on study treatment. Following lenalidomide discontinuation, subjects will be assessed at the 28-day Follow-up Visit for safety.

Second primary malignancies will be monitored as events of interest and should be included as part of the assessment of AEs throughout the course of the study. Investigators are to report any SPM as an SAE regardless of causal relationship to lenalidomide, occurring at any time for the duration of the study, from the time of signing the ICF/IAF until all subjects have been followed for up to 5 years from the last subject's first dose, unless consent is withdrawn, the subject is lost to follow-up or dies.

Overview of Pharmacokinetic Assessments

Blood samples for PK assessment will be collected from all subjects at specified time points (Table 3) for up to 24 hours on Cycle 1 Day 1 (Appendix H). Key PK parameters of plasma lenalidomide include apparent clearance and apparent volume of distribution. Effect of age and body size on lenalidomide PK will also be assessed.

Data Monitoring Committee

An external data monitoring committee (DMC) with multidisciplinary representation will be established to evaluate all available data and to ensure the ongoing safety of the subjects both currently receiving the study treatment and those still to be enrolled. The DMC will be comprised of medical oncologists with experience in treating pediatric subjects with AML and a statistician, all of whom are not otherwise involved in the study as Investigators. Following available treatment activity and safety data review, the DMC will advise on safety and treatment activity considerations and any other issues important to the conduct of the study and will make recommendations about the continuing safety of current participants and those yet to be enrolled. Once 4 subjects having received at least one dose of lenalidomide have completed at least 1 cycle of study treatment or discontinued treatment (whichever occurs first), the DMC will evaluate the safety data available 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 will meet at least semi-annually after sufficient subject data has been collected to review safety data. 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. Ad hoc DMC meetings may be scheduled if necessary.

Statistical Methods

All statistical analyses will be descriptive. There will be no formal statistical comparisons due to the single-arm study design and the small sample size. The first 43 subjects enrolled and evaluable for the primary endpoint analysis will be used to assess the primary endpoint.

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 final analysis, less than 8 of 43 evaluable subjects in both Stage 1 and Stage 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).

TABLE OF CONTENTS

TITLE PAGE 1
PROTOCOL SUMMARY 6
1. INTRODUCTION 23
1.1. Pediatric Acute Myeloid Leukemia 23
1.2. Treatment of Childhood Acute Myeloid Leukemia 23
1.3. REVLIMID® (Lenalidomide) 24
1.3.1. Lenalidomide Mechanism of Action 24
1.3.2. Lenalidomide Pharmacokinetics 25
1.3.2.1. Pharmacokinetics in Pediatric Populations 25
1.4. Rationale for Studying Lenalidomide in Relapsed/Refractory Pediatric AML 26
1.4.1. Adult High-Risk MDS and AML Trials 26
1.4.2. Lenalidomide Post-Allogeneic Stem Cell Transplant 27
1.4.3. Pediatric Studies 28
1.5. Summary 32
2. STUDY OBJECTIVES 33
2.1. Primary Objective 33
2.2. Secondary Objectives 33
3. STUDY ENDPOINTS 34
3.1. Primary Endpoint 34
3.2. Secondary Endpoints 34
4. OVERALL STUDY DESIGN 35
4.1. Study Design 35
4.2. Study Design Rationale 40
4.3. Starting Dose Rationale 40
4.4. Study Duration 41
4.5. End of Trial 41

5. TABLE OF EVENTS 42
6. PROCEDURES 48
6.1. Screening, Study Entry and Treatment Procedures 48
6.2. Administration of Intrathecal Cytarabine 48
6.3. Demographics and Medical History 48
6.4. Prior Medications/Procedures 49
6.5. Confirmation of Disease Relapse 49
6.6. Vital Signs 49
6.7. Physical Examinations 49
6.8. Pregnancy Testing and Pregnancy Risk and Lenalidomide Counseling 50
6.9. Performance Status 51
6.10. Echocardiography 51
6.11. Electrocardiogram 51
6.12. Height and Weight 51
6.13. Chest X-ray 51
6.14. Laboratory Assessments 51
6.14.1. Hematology Laboratory Assessments 52
6.14.2. Chemistry Laboratory Assessments 52
6.14.3. Urinalysis (dipstick) 52
6.15. Concomitant Medications/Procedures 52
6.16. IP Administration 53
6.17. IP Dispensing 53
6.18. IP Accountability 53
6.19. Information to be Collected on Screen Failures 54
6.20. Treatment Activity 54
6.20.1. Bone Marrow Aspirate or Biopsy and Peripheral Blood 54
6.20.3. Cytogenetics/FISH 55
6.20.4. Modified IWG Response 55
6.21. Safety 56
6.21.1. Adverse Events Reporting 56
6.21.2. Second Primary Malignancies 56

6.22. Treatment Discontinuation 57
6.23. Follow-up Phase 57
6.24. Optional Extension Phase 57
6.25. Investigational Product Specific Safety Concerns To Be Monitored or Assessed 57
6.26. Pharmacokinetic Sample Collection 59
6.26.1. Blood Collection for PK Analysis 59

7. STUDY POPULATION 62
7.1. Number of Subjects and Sites 62
7.2. Inclusion Criteria 62
7.3. Exclusion Criteria 65
7.4. Inclusion and Exclusion Criteria for OEP 66
8. DESCRIPTION OF STUDY TREATMENTS 67
8.1. Description of Investigational Product(s) 67
8.2. Treatment Administration and Schedule 67
8.2.1. Dose Reductions/Interruptions 69
8.2.2. Overdose 72
8.3. Method of Treatment Assignment 72
8.4. Packaging and Labeling 73
8.5. Investigational Product Accountability and Disposal 73
8.6. Investigational Product Compliance 73
9. CONCOMITANT MEDICATIONS AND PROCEDURES 74
9.1. Permitted Concomitant Medications and Procedures 74
9.2. Prohibited Concomitant Medications and Procedures 74
10. STATISTICAL CONSIDERATIONS 75
10.1. Overview 75
10.2. Study Population Definitions 75
10.3. Sample Size and Power Considerations 75
10.4. Background and Demographic Characteristics 76
10.5. Subject Disposition 76
10.6. Efficacy Analysis 76

10.6.1. Primary endpoint 76
10.6.2. Secondary endpoints 77
10.7. Safety Analysis 78
10.7.1. Toxicity Assessment 78
10.7.2. Adverse Events 78
10.7.3. Deaths 78
10.7.4. Clinical Laboratories 78
10.7.5. Vital Signs 78
10.9. Interim Analysis 79
10.9.1. Stopping Criteria for Acute Graft-Versus-Host Disease 80
10.9.2. Statistical Rationale for GVHD Stopping Criteria 80
10.10. Pharmacokinetic Analysis 80
10.11. Other Topics 80
11. ADVERSE EVENTS 81
11.1. Monitoring, Recording and Reporting of Adverse Events 81
11.2. Evaluation of Adverse Events 81
11.2.1. Seriousness 81
11.2.2. Severity/Intensity 83
11.2.3. Causality 84
11.2.4. Duration 84
11.2.5. Action Taken 84
11.2.6. Outcome 84
11.3. Abnormal Laboratory Values 84
11.4. Pregnancy 85
11.4.1. Female Children of Childbearing Potential and Females of Childbearing Potential 85
11.4.2. Male Subjects 86
11.5. Reporting of Serious Adverse Events 86
11.5.1. Safety Queries 86
11.6. Expedited Reporting of Adverse Events 87
12. DISCONTINUATIONS 88
12.1. Treatment Discontinuation 88

12.2. Study Discontinuation 88
13. EMERGENCY PROCEDURES 90
13.1. Emergency Contact 90
13.2. Emergency Identification of Investigational Products 90
14. REGULATORY CONSIDERATIONS 91
14.1. Good Clinical Practice 91
14.2. Investigator Responsibilities 91
14.3. Subject Information and Informed Consent 92
14.4. Confidentiality 92
14.5. Protocol Amendments 92
14.6. Institutional Review Board/Independent Ethics Committee Review and Approval 93
14.7. Ongoing Information for Institutional Review Board/Ethics Committee 93
14.8. Termination of the Study 93
15. DATA HANDLING AND RECORDKEEPING 95
15.1. Data/Documents 95
15.2. Data Management 95
15.3. Record Retention 95
16. QUALITY CONTROL AND QUALITY ASSURANCE 97
16.1. Study Monitoring and Source Data Verification 97
16.2. Audits and Inspections 97
17. PUBLICATIONS 98
18. REFERENCES 99
19. APPENDICES 105
Appendix A: World Health Organization Classification of Acute Myeloid Leukemia 105
Appendix B: Lenalidomide Dosing Table – Capsule 106
Appendix C: Lenalidomide Dosing Table – Oral Suspension 108
Appendix D: Modified International Working Group AML Response Criteria 110
Appendix E: KARNOFSKY PERFORMANCE STATUS 112
Appendix F: LANSKY PERFORMANCE STATUS 113
Appendix G: List of Abbreviations and Definitions of Terms 114
Appendix H: Lenalidomide Plasma* PK Sample Handling Instructions 119

Appendix I: Central Pathology Review 121

Appendix L: Optional Extension Phase 130

Appendix M: Tumor Lysis Syndrome 134

LIST OF TABLES

Table 1: Predicted Lenalidomide Plasma Exposure in Pediatric Subjects 41
Table 2: Table of Events 42
Table 3: PK Sampling Schedule During Cycle 1 Day 1 60
Table 4: Creatinine Clearance Estimation using the Schwartz Formula 63
Table 5: Age-based Cytarabine Dosing 69
Table 6: Dose Reductions of Lenalidomide 69

LIST OF FIGURES

Figure 1: Overall Study Design..... 39

1. INTRODUCTION

1.1. Pediatric Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is the most common acute leukemia in adults. Acute myeloid leukemia comprises approximately one-fifth of pediatric leukemias and is the seventh most common pediatric malignancy. The incidence rate is approximately 4 cases per 100,000. Approximately 500 children develop AML in the United States (US) per year with an incidence of pediatric AML in the US of 5.2 cases/million, peaking at 11 cases/million in children 2 years of age, with incidence decreasing until approximately 9 years of age then increasing to 9 cases/million during adolescence (Rubnitz, 2008; Rudant, 2008; Xie, 2003). Similar incidence rates across age groups for pediatric AML have been observed in Europe (Gatta, 2003; Marcos-Gragera, 2010). Although 90% of children with AML have no known risk factors, a number of predisposing constitutional disorders have been identified in the remaining 10% of children (Aplenc, 2000). Leukemia-associated genetic alterations, patterns of epigenetic changes, and rates of remission induction differ between pediatric and adult AML; although conventional AML therapy is essentially the same for adults and children (Tasian, 2014; Moore, 2013). Children generally have a relatively higher response rate to induction chemotherapy than adults, probably due to their superior ability to tolerate intensive multi-agent therapy, their lower prevalence of comorbidities and intensive supportive care remission (Tasian, 2014).

1.2. Treatment of Childhood Acute Myeloid Leukemia

Treatment of pediatric AML is generally divided into phases that are designed to induce remission and consolidate a disease-free post-remission status. Most chemotherapy regimens consist of the combination of 2 or 3 drugs, anthracycline and cytarabine, with the frequent addition of etoposide or 6-thioguanine. In a typical regimen, 2 intensive initial chemotherapy cycles are used to induce remission (Pui, 2004; Rubnitz, 2007) and consolidation therapy follows. Allogeneic hematopoietic stem cell transplantation (HSCT) may also be recommended for high-risk patients and is the only curative option (Rubnitz, 2007). Cytarabine and anthracyclines are gold standard agents for remission induction in patients of all ages. More than 90% of pediatric AML patients who undergo induction chemotherapy achieve complete remission (CR), however, relapse following primary therapy approaches 40%, and the 5-year event-free survival (EFS) rate is only approximately 50% (Creutzig, 2001; Stevens, 1998; Woods, 2001).

Treatment of children with AML remains unsatisfactory and outcomes are particularly poor for refractory and relapsed AML. Relapsed AML is associated with high morbidity and mortality and reinduction attempts are frequently unsuccessful (Tasian, 2014) and patients die of the disease or of treatment-related complications (Creutzig, 2012; Kaspers, 2005, Rubnitz, 2008). Although some patients with first relapse can achieve second remission (Sander, 2010), most patients in second and greater relapse will not achieve subsequent remission despite intensive cytotoxic chemotherapy. Of those patients achieving third remission, outcomes are dismal with long-term survivors reported only anecdotally (Gorman, 2010).

To date, treatment options for children with relapse or refractory AML (rrAML) generally include intensification of cytotoxic chemotherapy (including anthracyclines and cytarabine), HSCT, and supportive care (Shenoy, 2008; Sander 2010; Woods, 2001). Although these

therapies have led to improved outcomes in primary relapse, there remains little room for further treatment intensification in second or greater relapse due to the excess toxicities associated with cytotoxic chemotherapy such as infectious complications, end-organ dysfunction, and the high probability of bone marrow relapse despite HSCT (Tasian, 2014; Sander, 2010).

1.3. REVLIMID® (Lenalidomide)

REVLIMID® (lenalidomide) capsules are approved in the US and Canada for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities. In addition, REVLIMID, in combination with dexamethasone, is approved in the US and Canada for the treatment of patients with multiple myeloma (MM) who have received at least one prior therapy. In the US, REVLIMID is also approved for the treatment of patients with mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib. In addition, REVLIMID is approved in the US for newly diagnosed MM patients. To date, lenalidomide has been safely administered to over 300,000 patients across a wide variety of hematology and oncology diseases. Celgene sponsored and/or Investigator initiated trials (IIT) are currently studying lenalidomide in AML, non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), solid tumors, and in a number of pediatric oncology diseases.

A lenalidomide formulation for constitution to oral suspension has been developed. The oral suspension is available for use in subjects who are unable to swallow the capsules or at the discretion of the investigator. The lenalidomide oral suspension has demonstrated to be bioequivalent to the 25 mg capsule for a given dose. The magnitude of food effect on absorption of lenalidomide oral suspension is similar to that on the capsule formulation. The oral suspension of lenalidomide is not approved by any regulatory agency worldwide for any indication.

1.3.1. Lenalidomide Mechanism of Action

Lenalidomide is an immunomodulatory agent with a mechanism of action that includes anti-neoplastic, anti-angiogenic, pro-erythropoietic, and immunomodulatory properties. Specifically, lenalidomide inhibits proliferation and induces apoptosis of certain hematopoietic tumor cells (including MM plasma tumor cells, MCL and those with deletions of chromosome 5 [del(5q)] MDS in vitro). Lenalidomide causes a delay in tumor growth in some in vivo nonclinical hematopoietic tumor models including MM. Immunodulatory properties of lenalidomide include activation of T-cell and natural killer (NK) T-cell-mediated immunity and increases the number of NK T-cells, inhibits angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of microvessels (Lu, 2009), augments fetal hemoglobin production by CD34+ hematopoietic stem cells, and inhibits production of pro-inflammatory cytokines (eg, TNF-α and IL-6) by monocytes (Corral, 1999; Kotla, 2009). In MDS del(5q), lenalidomide was shown to selectively inhibit the abnormal clone by increasing the apoptosis of del(5q) cells (Pellagatti, 2007; Wei, 2009).

Lenalidomide binds directly to the protein cereblon (CRBN) encoded by the *CRBN* gene, which is part of an E3 ligase complex that includes deoxyribonucleic acid damage-binding protein 1 (DDB1), cullin 4 (CUL4) and regulator of cullins 1 protein (Roc1), and can inhibit the auto-ubiquitination of CRBN within the complex (Ito, 2010). E3 ubiquitin ligases are responsible for

the poly-ubiquitination of a variety of substrate proteins, including Ikaros (encoded by the gene *IKZF1*) and Aiolos (encoded by gene *IKZF3)*, targeting them for destruction in the proteasome. Ikaros and Aiolos are key transcription factors regulating immune cell development and homeostasis and degradation of these substrates by lenalidomide results in enhanced production of IL-2 and other cytokines known to regulate T-cell function. Therefore, the lenalidomide-induced reduction in Ikaros and Aiolos levels represents one possible mechanism of the pharmacological effects of lenalidomide, although other mechanisms may also play a role (Gandhi, 2014; Krönke, 2014; Lu, 2014). Altered activity of CRBN E3 ligase complexes may explain the broad cellular effects observed with lenalidomide treatment. Independent studies have confirmed the importance of CRBN in mediating the antiproliferative activity of lenalidomide in MM cells (Lopez-Girona, 2012; Zhu, 2011). Also, the importance of CRBN to the immunomodulatory activity of lenalidomide was demonstrated in human T-cells, as CRBN small interfering ribonucleic acid (siRNA) reduced lenalidomide-mediated increases in IL-2 and tumor necrosis factor –alpha (TNF-α) by ~60% (Report DM2528).

The mechanism of action of lenalidomide in AML has not yet been established and there have been few mechanistic studies in this indication. An in vitro evaluation of lenalidomide activity in a panel of AML cell lines showed that lenalidomide variably inhibited the viability of AML cell lines, and that this inhibitory effect of lenalidomide moderately correlated with cereblon expression levels (Report SF-ALM-0012). In del(5q) AML cells that have evolved from MDS patients, lenalidomide induced apoptosis via G2 cell cycle arrest (Wei, 2009). Lenalidomide may exert its effect by modulating cytokine levels in patients with AML as increases in interleukin-17 (IL-17) and macrophage colony-stimulating factor (M-CSF) levels were observed in responders to lenalidomide (combined with azaciditine treatment) (Pollyea, 2012). Finally, lenalidomide enhances the expression of an N-truncated isoform of C/EBPα, a transcription factor critical for normal myeloid cell differentiation. This causes an increase in *microRNA* (*miR)-181a* expression leading to strong inhibition of AML tumor growth and augmented sensitivity of leukemia cells to chemotherapy (Hickey, 2013). The importance of direct tumoricidal effects versus immunomodulatory effects of lenalidomide to anti-leukemic activity in patients remains to be elucidated.

1.3.2. Lenalidomide Pharmacokinetics

1.3.2.1. Pharmacokinetics in Pediatric Populations

The pharmacokinetics (PK) of lenalidomide have been evaluated in pediatric patients with solid tumors in two Phase 1 pediatric studies (Berg, 2011; Warren, 2011). A total of 47 pediatric patients were evaluated for PK in the two studies, with ages ranging from 4 to 21 years old. Doses studied were 20 to 116 mg/m^2/day for children with brain tumors, 15 to 70 mg/m^2/day for children with solid tumors, and 5 mg/m^2/day for children with MDS. In these pediatric patients, plasma lenalidomide exposure (AUC and C_{max}) increased approximately proportional to dose. The median time to reach the maximum concentration in plasma was approximately 1 to 4 hours following the oral administration and the mean terminal half-life ($t_{1/2}$) of lenalidomide was 2 to 3 hour in the two studies. These observations are consistent with those historically observed in adult patients with hematological malignancies including AML.

In pediatric patients ≥ 5 years of age, preliminary population PK analysis suggests that body weight is positively correlated with lenalidomide clearance and volume of distribution, but age has no effect.

The relationship between lenalidomide apparent total clearance (CL/F) and body size (weight or body surface area [BSA]) is not available for children younger than 5 years. Because gastrointestinal (GI) and renal functions reach the adult level by 1 year of age, oral absorption and renal elimination of lenalidomide is not anticipated to be highly age-dependent in patients 1 to 5 years. However, effects of the growth-dependent changes in the body size on lenalidomide clearance (plasma exposure) and volume distribution is expected in the 1 to < 5 year-old age group of pediatric patients. The impact of growth on plasma lenalidomide exposure has been taken into account when considering the weight-based dose for this study.

1.4. Rationale for Studying Lenalidomide in Relapsed/Refractory Pediatric AML

Approximately 5% of children with AML have refractory disease and about one-third to one-half of these pediatric patients relapse (Aplenc, 2000). The prognosis for a child with recurrent or progressive AML is generally poor (Webb, 1999; Wells, 2003) and AML at second or greater relapse represents an area of high unmet medical need for which novel strategies are needed to further improve outcomes. At relapse, pediatric patients are treated with salvage chemotherapy followed by allogeneic HSCT. However, side effects and toxicity still remain a major concern, hence the need for new agents (Creutzig, 2012). Lenalidomide is a novel, oral immunomodulatory agent, which has shown clinical activity in Phases 1 and 2 adult MDS and AML studies. These Phase 1 and Phase 2 adult studies have evaluated lenalidomide in subjects with and without del(5q) (Ades, 2009; Blum, 2010; Fehniger, 2009; Fehniger, 2011; Fenaux, 2011; List, 2006; Pollyea, 2012; Raza, 2008; Sekeres, 2010; Sekeres, 2011). Not only has lenalidomide shown single agent activity and acceptable tolerability at higher doses in adult high-risk MDS and AML without del(5q) (Blum, 2010; Fehniger, 2011), lenalidomide has established pediatric safety data from 2 completed Phase 1 studies (Berg, 2011; Warren, 2011).

1.4.1. Adult High-Risk MDS and AML Trials

Overall, lenalidomide monotherapy was relatively well tolerated at doses up to 50 mg/day given on Days 1 - 21 of a 28-day treatment cycle, in elderly patients with advanced AML (Blum, 2010; Fehniger, 2011). The observed safety profile was similar to that observed with lenalidomide treatment in patients with other hematological malignancies. No optimal dose or regimen could be established or concluded based on the available data.

In a Phase 1 dose-escalation trial in adults with relapsed or refractory leukemia, 31 patients with AML were treated with acceptable tolerability, a maximum tolerated dose (MTD) of 50 mg/day was established and a dose-limiting toxicity (DLT) of fatigue was observed at 75 mg/day. Five of 31 patients (16%) achieved complete remission and 3 patients of the 5 patients with cytogenetic abnormalities achieved cytogenetic CR (none of which was deletion 5q). Response duration ranged from 5.6 to 14 months. Notably, 2 patients who relapsed following allogeneic bone marrow transplantation achieved CR with lenalidomide (Blum, 2010).

A Phase 2 study of high-dose lenalidomide as initial therapy for newly-diagnosed elderly AML patients (age > 60 years) evaluated the response to lenalidomide 50 mg daily for two, 28-day

cycles followed by low-dose maintenance therapy (10 mg daily) for up to 12 cycles (Fehniger, 2011). Of the 33 patients enrolled, the CR/complete remission with incomplete blood count recovery (CRi) rate was 30% (CRi defined as CR with insufficient hematological recovery of platelets or neutrophils) and was 53% for the 19 patients completing at least 2 cycles of high-dose 50 mg lenalidomide. Median time to CR/CRi was 30 days (range 1 to 72 days) and median duration of CR/CRi was 10 months. The response rate and toxicity profile are favorable compared to other low-intensity agents (Fehniger, 2011).

Responses to lenalidomide have been observed in patients with high-risk MDS and AML with del(5q). In a Phase 2 study of 47 high-risk MDS patients, most of whom had complex cytogenetics, the response rate was 28% with lenalidomide 10 mg/day (Raza, 2008). In the Phase 2 Southwest Oncology Group Study (SWOG) S0605 study, 37 elderly AML patients with del(5q) were treated with lenalidomide 50 mg daily for 28 days as induction therapy and 10 mg daily for 21 days of a 28-day cycle as maintenance. Fourteen patients (38%) completed induction therapy and 8 (22%) started maintenance. Five of the 37 total patients (14%) achieved a partial or complete response, two with isolated del(5q) and 3 with complex cytogenetics. Median relapse-free survival for responders was 5 months (range, 0 to 19 months) (Sekeres, 2011).

In a Phase 2 IIT by Pollyea and colleagues (Pollyea, 2012), untreated AML patients ineligible for conventional chemotherapy received azacitidine 75 mg/m^2/day on Days 1 - 7 followed by escalating doses of lenalidomide up to 50 mg/day on Days 8 - 28 of 42-day cycles. Treatment was continued until progression of disease, unacceptable adverse event (AE) or completion of 12 cycles. Among 42 evaluable patients, the overall response rate (ORR) was 41%, with 28% of patients achieving a complete response (CR/CRi). The median time to CR/CRi was 12 weeks (range, 6 to 18 weeks); the median duration of response (CR/CRi/PR) was 28 weeks (range 6 to > 104 weeks). Median overall survival (OS) for all patients in the study was 20 weeks (range, 1 to > 121 weeks) and 69 weeks (range, 10 to > 121 weeks) for patients who responded to therapy. Additionally, median overall survival for responders was superior to non-responders (69 versus 15 weeks $p < 0.01$) (Pollyea, 2012).

In general, AEs encountered with the use of lenalidomide in the treatment of AML and high-risk MDS are similar to those observed in patients treated with lenalidomide for other hematological malignancies. The most common hematological Grade 3 or higher AEs were neutropenia and thrombocytopenia. The most common Grade 3 or higher non-hematological AEs were fever or infection, fatigue, and dermatological toxicities including rash (Chen, 2013).

1.4.2. Lenalidomide Post-Allogeneic Stem Cell Transplant

Two adult studies utilizing lenalidomide as maintenance therapy following allogeneic HSCT in MM both reported a high rate of induction of graft versus host disease (GVHD) (Kneppers, 2011; Sockel, 2011). Although this high rate of GVHD was associated with a patient population in remission, lenalidomide showed efficacy with tolerable GVHD when studied in relapsed MM and relapsed AML patients previously treated with allogeneic HSCT (Ades, 2010; Bensinger, 2012; El-Cheikh, 2012; Ford, 2010; Lioznov, 2010; Montefusco, 2012). Additionally, GVHD rash has been reported in relapsed adult AML/MDS and MM patients after achieving CR with lenalidomide post allogeneic HSCT (Blum, 2010; Ford, 2010). This observation suggests that the immune modulatory effects of lenalidomide activate a graft-versus-leukemia effect and may

be particularly beneficial in the control of the disease that has relapsed after allogeneic HSCT. A case-matched retrospective analysis comparing lenalidomide after autologous or after allogeneic HSCT confirmed this hypothesis by demonstrating a survival advantage in allografted myeloma patients (Montefusco, 2012).

The primary objective of this study is to determine the activity of lenalidomide in pediatric patients with relapsed/refractory AML (with second or greater relapse or refractory to at least 2 prior induction attempts). Treatment of an AML recurrence following allogeneic HSCT commonly includes a rapid taper of immune-suppression used for prophylaxis and/or treatment of acute GVHD. In this setting, mild GVHD is an expected and a desirable toxicity. The use of the immune-modulatory drug, lenalidomide, in patients at risk for acute GVHD will be challenging but with the potential for benefit to the patient with induction of mild but manageable GVHD. Accordingly, this study will attempt to keep patients with new mild GVHD on protocol therapy, while recognizing that Grade 3 or greater acute GVHD will be an unacceptable toxicity. First, patients with active GVHD or requiring immune-suppression including steroids for GVHD control are not eligible for enrollment. Patients with a history of Grade 3 or greater GVHD or those on therapeutic dosing of immune suppressive therapy will be discussed with the study chair prior to enrollment and require a longer observation time off immune-suppression prior to enrollment (4 weeks) compared to those without a history of severe GVHD or who are already on tapering dosing of immune suppressive therapy without signs of GVHD (2 weeks off immune-suppression) (see Sections 6.25, 7.2 and 8.2.1). Second, patients who develop Grade 3 or greater GVHD, or lower grade GVHD that does not respond to protocol prescribed interventions (Section 8.2.1) will be off study treatment. No dose reduction is planned as it is not clear that this toxicity would improve and be altered by dose adjustment. Incidence of GVHD will be closely monitored and the study will be closed to post-HSCT patients if stopping thresholds for Grade 3 or greater GVHD are crossed (see Section 10.9.1). Patients will be monitored for development of chronic GVHD.

1.4.3. Pediatric Studies

In a Phase 1 study of lenalidomide performed by the [redacted] in pediatric patients with relapsed or refractory solid tumors or MDS, 49 subjects were treated with dosages up to 70 mg/m^2/day for 21 days of a 28-day cycle. Six DLTs were observed, which were sporadic and not clearly associated with the dose. These DLTs included Grade 3 hypercalcemia (15 mg/m^2/day), Grade 3 hypophosphatemia (40 mg/m^2/day), Grade 3 hypokalemia (40 mg/m^2/day), Grade 4 neutropenia (40 mg/m^2/day), Grade 3 somnolence (40 mg/m^2/day), and Grade 3 urticaria (55 mg/m^2/day). These DLTs occurred at doses ranging from 15 mg/m^2/day to 55 mg/m^2/day. There were no DLTs reported among the 6 patients enrolled at 70 mg/m^2/day and the MTD was not reached (Berg, 2011). At the 25 mg/m^2/day dose, 1 patient had a cerebrovascular ischemic event of uncertain relationship to lenalidomide.

A second Phase 1 trial of lenalidomide in pediatric patients with recurrent, refractory or progressive CNS tumors was performed by the Pediatric Brain Tumor Consortium (Warren, 2011). In the 44 evaluable patients, treated at doses of 15 to 116 mg/m^2/day for 21 days of a 28-day cycle, the MTD was not reached. A total of 34 patients received more than 1 course of therapy, 23 patients received more than 6 courses, and 10 patients received more than 12 courses. Lenalidomide was well-tolerated in these patients and myelosuppression, a known toxicity in adult patients, was the major toxicity observed in this study population. Other common toxicities

included fatigue (30%), GI symptoms including nausea (10%), emesis (4%), diarrhea (16%), and constipation (8%), as well as rash (14%) and muscle cramping (10%). There was no clear dose relationship with these acute toxicities. Of note, 2 patients experienced DLTs. The first patient, treated at the 20 mg/m^2/day dose level had a presumed myocardial infarction and elevated troponin in the setting of multiple risk factors for thromboembolism. A second patient experienced a DLT of Grade 4 fatigue at the 68 mg/m^2/day dose level. Antitumor activity, defined by both objective responses and long-term stable disease, was observed in 2 of 51 patients, both with low-grade gliomas (Warren, 2011).

Neither of these 2 completed pediatric Phase 1 studies of lenalidomide reached an MTD with one stopping at 70 mg/m^2/day for 21 days of a 28-day treatment cycle (Berg, 2011), and the other stopping at 116 mg/m^2/day for 21 days of a 28-day treatment cycle (Warren, 2011). While these studies were performed in subjects with solid tumors, they demonstrate that high doses of lenalidomide are well-tolerated in children.

Currently, a randomized Phase 2 study (n = 80 planned) of lenalidomide (low dose: 20 mg/m^2/day versus high dose: 115 mg/m^2/day) in children with recurrent, refractory, or progressive juvenile pilocytic astrocytomas and optic pathway gliomas is ongoing (COG Study Number ACNS1022 and clinicaltrials.gov identification number NCT01553149).

1.5. Summary

Treatment of pediatric rrAML remains an unmet medical need due to the low likelihood of achieving clinical benefit from existing therapies and limited long-term survival. Thus, given lenalidomide's activity in adults with AML and tolerability in children, a study of lenalidomide in pediatric AML subjects with relapsed or refractory disease (with second or greater relapse or refractory to at least 2 prior induction attempts) will generate beneficial information in the treatment of this subject population.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is:

- To determine the activity of lenalidomide in the treatment of pediatric subjects with relapsed/refractory AML (with second or greater relapse or refractory to at least 2 prior induction attempts) measured by morphological complete response defined as either a CR or CRi within the first 4 cycles of treatment.

2.2. 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, duration of response (DoR) 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.

3. STUDY ENDPOINTS

3.1. Primary Endpoint

- Morphologic complete response rate (CR or CRi) within the first 4 cycles of treatment with lenalidomide.

3.2. Secondary Endpoints

- Durable response rate.
- Duration of response (DoR).
- 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. OVERALL STUDY DESIGN

4.1. Study Design

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 70 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 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 AML to warrant subsequent study.

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

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 second primary malignancies (SPMs) will be monitored (Table 2).

An external DMC will evaluate safety and treatment activity data in an ongoing and 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. Once 4 subjects having received at least one dose of lenalidomide have completed at least 1 cycle of study treatment or discontinued treatment (whichever occurs first), the DMC will evaluate the safety data available 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 underlying principles for the DMC are ethical and safety aspects for the subjects. It will be the task of the DMC to examine whether the conduct of the study is still ethically justifiable, whether security of the subjects is ensured, and whether the process of the study is acceptable. For this, the DMC has to be informed about the adherence to the protocol, the subject accrual, and any observed AE(s). The composition and responsibilities of the DMC, including the structure and procedures of its meetings, will be outlined in a DMC charter.

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

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.

As part of the screening procedures, a fresh bone marrow aspirate and/or a bone marrow biopsy paraffin embedded slide will be collected from all subjects for confirmation of disease. The confirmation of disease will be performed locally.

A standard cytogenetic metaphase preparation from the fresh BMA must be prepared for the cytogenetic testing/chromosome analysis including karyotype. The local site will submit the reports of the karyotype, FISH studies, as well as any available data on molecular mutations (FLT3, CEPBa, NPM1, and others including exome sequencing via Foundation Medicine or other sources) if performed, to the central reviewer at . If subjects have a FISH detectable marker, the test should be repeated until CR/CRi and at relapse.

The BMA slide (and/or bone marrow biopsy embedded paraffin slide) and peripheral blood smear from screening **must** be provided to the central reviewers at . The central review will provide standardized analysis and reporting for all subjects. The central reviewer's assessment will be used retrospectively to confirm diagnosis.

Creatinine clearance (CLcr) will be measured at screening using Table 4 (see Section 7.2).

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 as per the Investigator may continue to receive lenalidomide in an OEP (Appendix L) 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 (Table 6). 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. For additional details regarding dose reductions and dose capping see Section 8.2.1.

During the Treatment Phase, subjects will be assessed for treatment activity based on modified IWG AML Response Criteria (Appendix D). To determine morphologic CR/CRi, BMA/biopsy and peripheral blood smear must be collected from all subjects at the completion of the 21-day treatment period of the predefined treatment Cycles 1, 2, 3 and 4 within 6 days **before dosing for each subsequent cycle** (ie, between Day 22 to Day 27 of that cycle) (Table 2). If morphologic CR/CRi is achieved within the first 2 cycles, BMA/biopsy and peripheral blood smear will not be required at the end of Cycle 3. For all subjects, BMA/biopsy and peripheral blood smear must be performed at the completion of Cycle 4, and at the Treatment Discontinuation Visit or at the time of suspected relapse (whichever occurs first). For subjects who are assessed as having partial response, the BMA/biopsy and peripheral blood smear will be repeated at Cycle 8 unless the subject goes to allogeneic HSCT, and at the Treatment Discontinuation Visit or at the time of suspected treatment failure (whichever occurs first). ***A bone marrow biopsy is required only if a bone marrow aspirate cannot be obtained***. Subjects demonstrating clinical benefit as per the Investigator at the end of Cycle 4 and beyond may continue to receive lenalidomide on study for up to 12 cycles in the absence of protocol-defined toxicity or transitioning to allogeneic HSCT.

During the study, repeat of local testing of bone marrow cytogenetics and FISH for any positive markers is to be completed whenever a BMA/biopsy is obtained. However, if the cytogenetics/FISH results are 'normal' at screening or at any point during the study, cytogenetic analysis is not required to be repeated except at the Treatment Discontinuation Visit or at the time of bone marrow evaluation for suspected relapse (whichever occurs first).

In order to establish lenalidomide plasma PK parameters in subjects with rrAML, blood samples will be collected at specified time points (Table 3) for up to 24 hours postdose from all enrolled subjects during Cycle 1 Day 1 (Instructions for PK sample handling are in Appendix H).

Dose interruptions, delays and modifications may be required to manage adverse events (AEs) during study treatment (see Section 8.2.1 for details). In order to optimally benefit from protocol-prescribed therapy, the Investigator should aim to treat subjects for **at least 4 cycles** with lenalidomide. Subjects demonstrating clinical benefit as per the Investigator at the end of Cycle 4 and beyond may continue to receive lenalidomide on study up to 12 cycles in the absence of protocol-defined toxicity or transitioning to allogeneic HSCT. Subjects may be

treated beyond 12 cycles of study treatment in the OEP if they continue to benefit and have not undergone HSCT.

Subjects may be discontinued from the treatment at the Investigator's discretion for any of the reasons as detailed in Section 12. All discontinued subjects, regardless of reason for discontinuation, should undergo treatment discontinuation procedures at the time of investigational product (IP) discontinuation (Table 2). The reason for discontinuation will be recorded in the electronic case report form (CRF) and in the source document.

An interim analysis is planned to take place 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. The interim analysis will assess the number of subjects with CR or CRi under lenalidomide treatment.

Follow-up Phase

Subjects will enter the Follow-up Phase at the time of permanent discontinuation of 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 (see Section 6.8 and Section 7.2).

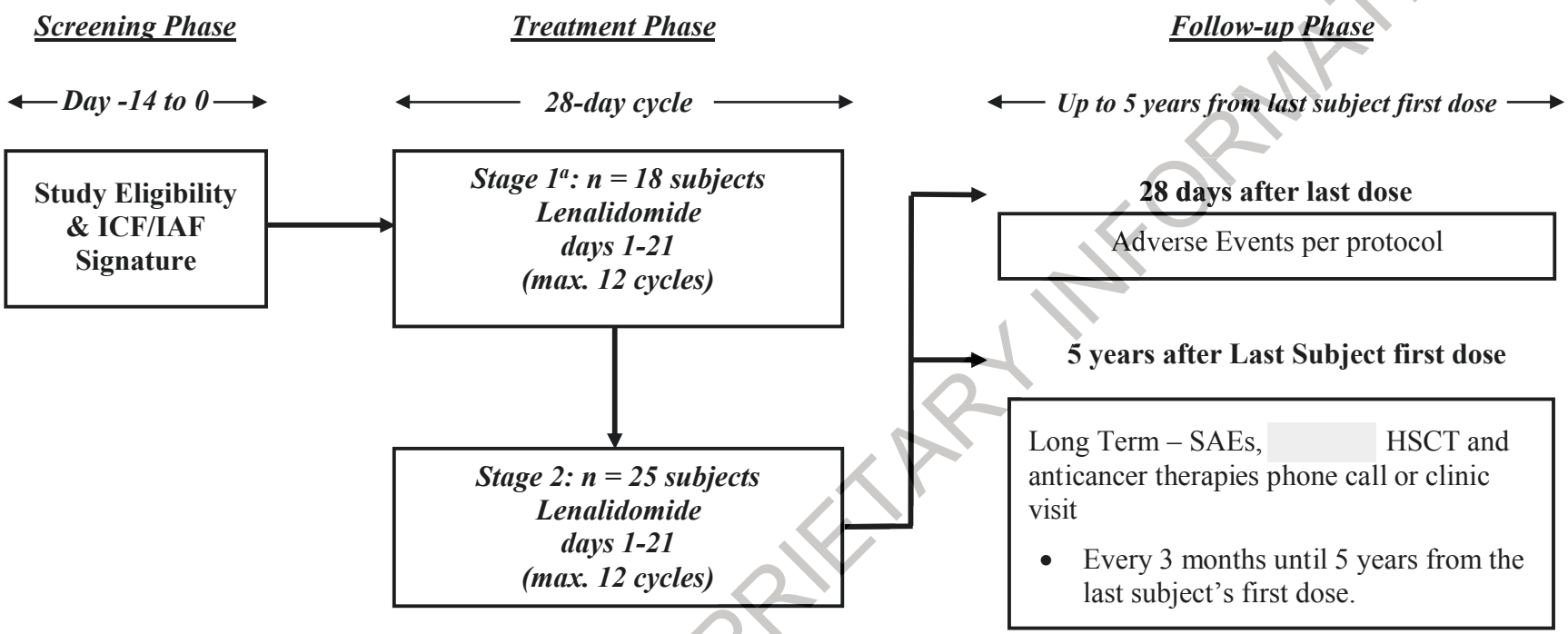
After the 28-day Follow-up Visit, subjects will be followed up by phone or clinic visit, whichever is the institution's normal standard of care, every 3 months for a maximum of 5 years from the last subject's first dose, regardless of new anticancer treatment or HSCT, for SPMs, safety issues (any drug-related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

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 (see Section 12) may enter the optional extension phase (OEP).

Details for the OEP are provided in Appendix L.

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 Design Rationale

The main objective of the proposed study is to establish the preliminary activity of lenalidomide in pediatric subjects with rrAML, specifically looking at the morphologic complete response, defined as either CR or CRi, within the first 4 cycles of lenalidomide treatment.

The present study is a Phase 2 study based on Simon's Optimal two-stage design enabling assessment of the overall response rate (ORR) in this subset of pediatric subjects while providing the opportunity of early stopping in the event of lack of activity with regards to the ORR being observed.

4.3. Starting Dose Rationale

The proposed initial starting dose for pediatric patients with relapsed or refractory AML aims to produce daily plasma AUC close to that observed in adult AML patients treated with lenalidomide at 50 mg/day dose. Data from 2 pediatric Phase 1 studies conducted by and the Pediatric Brain Tumor Consortium demonstrate that lenalidomide is well-tolerated at doses up to 116 mg/m^2/day (Berg, 2011; Warren, 2011). Pharmacokinetic data from the study indicate that the PK parameters in the pediatric subjects (5 to 18 years of age) were generally similar to those in adult patients (Berg, 2011). However, the effect of the growth-dependent changes in the body size on lenalidomide clearance (plasma exposure) and volume distribution is expected in the 1 to < 5-year-old age group of pediatric patients. The impact of growth on plasma lenalidomide exposure has been taken into account when considering the weight-based dose for this study.

Since two Phase 1 pediatric studies have demonstrated that lenalidomide safety profiles in pediatric patients are similar to those observed in adult patients (Berg, 2011; Warren, 2011), the pediatric AML dose in this proposed study was extrapolated from the adult lenalidomide experience in AML trials. Both the MTD and the active dose of lenalidomide is 50 mg/day in adult AML subjects. Thus, a lenalidomide dose that produces plasma AUC level approximating the AUC in adult AML subjects treated with 50 mg/day is considered a reasonable initial starting dose for this pediatric study.

By combining available data from pediatric and adult subjects, a population PK model that incorporates the impact of body weight on lenalidomide clearance and volume of distribution was developed. Monte Carlo simulations were conducted using the fixed and random effect parameters from this population PK model to predict lenalidomide plasma exposure parameters at the dose proposed for pediatric subjects. As summarized in Table 1, the predicted mean AUC_∞ in pediatric subjects > 5 years of age would be close to the target AUC. Although the predicted AUC for subjects 1 to < 5 years old was slightly lower, the predicted C_{max} is similar to that of adult AML subjects. Since the activity of lenalidomide was also observed at a lower dose of 25 to 35 mg/day in adult AML subjects (Blum, 2010), the lenalidomide exposure at 2 mg/kg/day is expected to remain within the therapeutic range for the age group of 1 to < 5 years. The safety profile of high-dose lenalidomide remains largely unknown for the age group of < 5 years and a conservative approach (ie, slightly lower AUC) is considered the most acceptable approach.

Table 1: Predicted Lenalidomide Plasma Exposure in Pediatric Subjects

Lenalidomide Dose	Study Population	AUC_{∞} (h*ng/mL)	C_{max} (ng/mL)
2 mg/kg, not exceeding 70 mg/day	Pediatric patients		
	1 to < 2 years	3029 (25.7)	758 (19.2)
	2 to < 3 years	3461 (25.1)	852 (18.6)
	3 to < 4 years	3855 (24.9)	944 (18.5)
	4-5 years	4420 (32.7)	1069 (26.5)
	6-11 years	5871 (30.7)	1343 (23.7)
	12-18 years	5988 (26.0)	1222 (21.9)
50 mg/day	AML adults	5509 (37.9)	946 (40.4)

AML = acute myeloid leukemia; AUC_{∞} = area under the plasma concentration-time curve from time zero extrapolated to infinity; C_{max} = maximum plasma concentrations.
Data for pediatric population are predicted from the population PK model and expressed as geometric mean (geometric CV%); data for AML adults are from literature (Blum, 2010) and expressed as mean (CV%).

4.4. Study Duration

Enrollment is expected to last approximately 40 months with an accrual rate of 1 to 2 subjects per month. Once 4 subjects having received at least one dose of lenalidomide have completed at least 1 cycle of study treatment or discontinued treatment (whichever occurs first), the DMC will evaluate the safety data available and provide a recommendation. At the end of Stage 1 and following safety and treatment activity data review, the DMC will 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. Subjects demonstrating clinical benefit as per the Investigator at the end of Cycle 4 and beyond may continue to receive lenalidomide on study up to 12 cycles in the absence of protocol-defined toxicity or transitioning to allogeneic HSCT. Once lenalidomide has been discontinued, subjects will be followed up to 5 years from the last subject's first dose, unless consent is withdrawn, the subject is lost to follow-up or dies.

4.5. 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, or the date of receipt of the last data point from the last subject that is required for primary, secondary analysis, as prespecified in the protocol, whichever is the later date.

5. TABLE OF EVENTS

Table 2: Table of Events

Procedure	Screening Phase Day -14 to 0	Treatment Phase[a]																OEP[β]	Treatment Discontinuation	Follow-up Phase[a]	
		Cycle 1						Cycle 2				Cycle 3		Cycle 4		Cycle 5-12				28-day	LT F/U
		Day						Day				Day		Day		Day					
		1	2	4	8	15	22	1	8	15	22	1	22	1	22	1	22				
Study Entry Assessment																					
Informed consent/assent (ICF/IAF)	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Inclusion/Exclusion Evaluation	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Demographics	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Medical History	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
12-Lead ECG[b]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Urinalysis[b]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Chest X-ray[c]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Prior Treatments and Medications[d]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lansky/Karnofsky Performance Status	X	X	-	-	-	-	-	X	-	-	-	X	-	X	-	X	-	-	X	-	-
Echocardiography	X	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-	X[e]	-	X	-	-
Confirmation of rrAML[f]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Enrollment	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 2: Table of Events (Continued)

Procedure	Screening Phase Day -14 to 0	Treatment Phase[a]																		Follow-up Phase[a]	
		Cycle 1						Cycle 2				Cycle 3		Cycle 4		Cycle 5-12		OEP[β]	Treatment Discontinuation	28-day	LT F/U
		Day						Day				Day		Day		Day					
		1	2	4	8	15	22	1	8	15	22	1	22	1	22	1	22				
Safety Assessment																					
Adverse Events	After signing ICF/IAF and until 28-day Follow-up Visit																				-
Assessment of Second Primary Malignancy[g]	After signing ICF/IAF and for 5 years from last subject, first dose																				
Physical Examination (including Vital Signs)[b]	X	X	-	-	X	X	X	X	-	X	-	X	-	X	-	X	-	-	X	X	-
Height	X	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Body Weight	X	X	-	-	-	-	-	X	-	-	-	X	-	X	-	X	-	-	-	-	-
Hematology (including Manual Differential with Blast count)[h]	X	X	-	-	X	X	X	X	X	X	X	X	-	X	-	X	-	-	X	X	-
Serum Blood Chemistry[h]	X	X	X	X	X	X	X	X	X	X	X	X	-	X	-	X	-	-	X	X	-
Serum Pregnancy Testing (FCCBP/FCBP)[i]	X	X	-	-	X	X	X	X	-	-	-	X	-	X	-	X	-	X	X	X	-
Lenalidomide Counseling[j]	X	X	-	-	-	-	-	X	-	-	-	X	-	X	-	X	-	X	X	X	-
Concomitant Medications and Procedures[k]	After signing ICF/IAF and until 28-day Follow-up Visit																				-

Table 2: Table of Events (Continued)

Procedure	Screening Phase Day -14 to 0	Treatment Phase[a]																		Follow-up Phase[a]	
		Cycle 1						Cycle 2				Cycle 3		Cycle 4		Cycle 5-12		OEP[β]	Treatment Discontinuation	28-day	LT F/U
		Day						Day				Day		Day		Day					
		1	2	4	8	15	22	1	8	15	22	1	22	1	22	1	22				
IP Administration and Compliance																					
IP dispensing[l]	-	X	-	-	-	-	-	X	-	-	-	X	-	X	-	X	-	X	-	-	-
IP accountability[m]	-	X	-	-	-	-	-	X	-	-	-	X	-	X	-	X	-	X	X	-	-
Treatment Activity Assessment																					
Bone Marrow Aspirate	X[n,q]	-	-	-	-	-	X[r]	-	-	-	X[r]	-	X[r]	-	X[r]	-	X[r,s]	-	X[u]	-	-
Bone Marrow Biopsy[o]	X[n,q]	-	-	-	-	-	X[r]	-	-	-	X[r]	-	X[r]	-	X[r]	-	X[r,s]	-	X[u]	-	-
Peripheral Blood smear (CBC + Cytology) Sampling	X[q]	-	-	-	-	-	X[r]	-	-	-	X[r]	-	X[r]	-	X[r]	-	X[r,s]	-	X[u]	-	-
IWG Response Assessment	-	-	-	-	-	-	X[r]	-	-	-	X[r]	-	X[r]	-	X[r]	-	X[r,s]	-	X[u]	-	-
Cytogenetic Testing/ FISH[p,t]	X	-	-	-	-	-	X	-	-	-	X	-	X	-	X	-	X	-	X[u]	-	-
Follow-up Anticancer Therapies	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X
SAE, HSCT Follow-up	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X

Table 2: Table of Events (Continued)

Procedure	Screening Phase Day -14 to 0	Treatment Phase[a]																		Follow-up Phase[a]	
		Cycle 1						Cycle 2				Cycle 3		Cycle 4		Cycle 5-12		OEP[β]	Treatment Discontinuation	28-day	LT F/U
		Day						Day				Day		Day		Day					
		1	2	4	8	15	22	1	8	15	22	1	22	1	22	1	22				
Other Assessments																					
PK Sampling (blood)[z]	-	X	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Intrathecal (IT) Cytarabine[α]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
OEP Eligibility Criteria[β]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-	-

AE = adverse event; AML = acute myeloid leukemia; BMA = bone marrow aspirate; CBC = complete blood count; CNS = central nervous system; ; CRF = case report form; CR = complete response; CRi = CR with incomplete blood count recovery; CSF = cerebrospinal fluid; ECG = electrocardiogram; FCBP = Female of Childbearing Potential; FCCBP = Female Children of Childbearing Potential; FISH = Fluorescent In Situ Hybridization; F/U = follow-up; HSCT = hematopoietic stem cell transplantation; IAF = informed assent form; ICF = informed consent form; IP = investigational product; IT = intrathecal; IWG = International Working Group; ; LT = long term; ; OEP = Optional Extension Phase; ; PK = pharmacokinetics; rrAML = relapsed/refractory acute myeloid leukemia; SAE = serious adverse event; SPM = second primary malignancy.

[a] Study visit window is ± 3 days in the Treatment Phase, unless noted otherwise for a particular assessment. Study visit windows should take into account the subject's investigational product supply. Only enough lenalidomide for 1 cycle of therapy will be dispensed with each cycle of therapy. In the Follow-up Phase, the study visit window is ± 7 days.

[b] Additionally, ECG, urinalysis, and physical exam (including vital signs) can be performed at any unscheduled visits (only if clinically indicated).

[c] Chest X-ray is not needed if a previous chest X-ray taken within 4 weeks prior to Day 1 of Cycle 1 is available and not clinically significant, otherwise a chest X-ray will be performed at screening.

[d] All prior medications/procedures (including chemotherapy, cytotoxic therapy, radiotherapy and HSCT) related to AML or any malignancy, and received at any point in the subject's history, should be recorded on the CRF at screening, regardless of time. All other prior medications/procedures used within 14 days of signing the ICF/IAF should also be recorded.

[e] An echocardiogram will be performed at screening, at the end of Cycles 4 and 12 and at the Treatment Discontinuation Visit.

[f] All dates of relapse and/or refractory diagnosis should be recorded (at least 2 required). Disease relapse (rrAML) will be retrospectively confirmed by a central reviewer at screening.

[g] Second primary malignancies will be monitored as events of interest and must be reported as SAE's. This includes any SPM, regardless of causal relationship to lenalidomide.

[h] Hematology and chemistry assessments will be conducted **locally**. Whenever a hematology sample is collected for a CBC, a peripheral blood smear (Cytology) will be used to assess a manual blood count differential including blast count. Only select analytes will be recorded in the CRF.

[i] Female Children of Childbearing Potential is defined as females who have achieved menarche and/or breast development in Tanner stage 2 or greater, and have not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries). Note: Amenorrhea following cancer therapy does not rule out childbearing potential. Female of Childbearing Potential is defined as a sexually mature woman who has not undergone a hysterectomy or bilateral oophorectomy, has not been naturally postmenopausal (amenorrhea following cancer does not rule out childbearing potential) for at least 24 consecutive months.

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for FCCBP/FCBP, including those who commit to complete abstinence. FCCBP/FCBP must have 2 negative pregnancy tests (with sensitivity of at least 25 mIU/mL) prior to starting lenalidomide. The first pregnancy test must be performed within 10 - 14 days prior to the start of lenalidomide and the second pregnancy test must be performed within 24 hours prior to the start of lenalidomide.

NOTE: The pregnancy test 10 to 14 days prior to initiation of lenalidomide may be omitted, at the discretion of the investigator, for any FCCBP/FCBP who has high acuity disease requiring immediate treatment with lenalidomide. The pregnancy test within 24 hours prior to the first dose of lenalidomide is required to be performed.

FCCBP/FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at day 28 following IP discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and at days 14 and 28 following IP discontinuation. The subject may not receive lenalidomide until the Investigator has verified that the result of the pregnancy test performed on Day 1 of every cycle is negative.

[j] Subjects (FCCBP/FCBP) must be counseled about pregnancy precautions and risks of fetal exposure at a minimum of every 28 days. They must also be counseled against sharing lenalidomide and donating blood, semen or sperm during therapy and within 28 days after Treatment Discontinuation. Pregnancy counseling and potential risks must be conducted on Day 1 of each cycle prior to lenalidomide dispensing.

[k] All concomitant over-the-counter/prescription medications/procedures, and intravenous medications taken from signing of the informed consent up to 28 days after the last dose of lenalidomide must be recorded on the appropriate CRF.

[l] Lenalidomide should be dispensed on Day 1 of each cycle. Only enough lenalidomide for 1 cycle of therapy will be dispensed with each cycle of therapy. The first dose of lenalidomide should be taken only after all Day 1 procedures have been completed with the exception of the collection of PK sampling.

[m] Lenalidomide accountability should be assessed before IP dispensing for each treatment cycle.

[n] A fresh bone marrow aspirate (and/or a fresh bone marrow biopsy paraffin embedded slides) will be collected at screening from all subjects for confirmation of relapsed/refractory disease.

[o] ***A bone marrow biopsy is required only if a bone marrow aspirate cannot be obtained***.

[p] A standard cytogenetic metaphase preparation from the fresh BMA must be prepared for the local cytogenetic testing/chromosome analysis including karyotype. The local site will submit the reports of the karyotype, FISH studies, as well as any available data on molecular mutations (FLT3, CEPBa, NPM1, and others including exome sequencing via Foundation Medicine or other sources) if performed to the central reviewer for retrospective review at Screening only. If subjects have a FISH detectable marker, the test should be repeated until CR/CRi and at relapse.

[q] The screening BMA slide (and/or bone marrow biopsy paraffin embedded slide) and peripheral blood smear slide **must** be provided to the central reviewers at the The central review will provide standardized analysis and reporting for all subjects. The central reviewer's assessment will be used retrospectively to confirm diagnosis. In the case where a study center has an IRB- and Celgene-approved procedural ICF/IAF that allows collection of additional bone marrow samples for potential research purposes, the latest pre-study PB and BM aspirate/biopsy may be used for screening study assessments.

[r] BMA/biopsy and peripheral blood smear must be collected at the completion of the 21-day treatment period within 6 days **before dosing for the subsequent cycle** (ie, between Day 22 to Day 27 of that cycle) in Cycles 1, 2, 3 and 4. If morphologic CR/CRi is achieved within the first 2 cycles, the BMA/biopsy and peripheral blood smear will not be required at the end of Cycle 3. These assessments are required for all subjects at the end of Cycle 4, and at the Treatment Discontinuation Visit or at the time of suspected relapse (whichever occurs first). An IWG response assessment will be performed whenever a bone marrow assessment is performed.

[s] For subjects who are assessed as having partial response, the BMA/biopsy and peripheral blood smear will be repeated at Cycle 8 unless the subject goes to allogeneic HSCT, and at the Treatment Discontinuation Visit or at the time of suspected treatment failure (whichever occurs first).

[t] During the study, repeat of bone marrow local cytogenetic/FISH testing is to be completed whenever a bone marrow aspirate/biopsy is obtained. However, if the cytogenetics/FISH results are 'normal' at screening or at any point during the study, no further cytogenetic/FISH analysis is required, except at the Treatment Discontinuation Visit or at the time of relapse (whichever occurs first).

[u] Bone marrow aspirate/biopsy, peripheral blood smear, cytogenetic testing, and an IWG response assessment will be measured at the Treatment Discontinuation Visit or at the time of suspected relapse (whichever occurs first). If clinically inappropriate per the treating site, the subject may have bone marrow evaluation omitted if peripheral blast results are collected.

[z] Blood PK sampling time points are specified in Table 3.

[α] As per routine standard of care, intrathecal cytarabine (age-based dosing) will be administered to all subjects within 2 weeks prior to administration of lenalidomide. For subjects **without CNS involvement**, subsequent intrathecal chemotherapy may be administered at the discretion of the treating physician. For subjects with **CNS involvement at screening**, intrathecal cytarabine will be administered ***twice weekly x 4 doses*** and until CSF is clear on 2 consecutive evaluations for up to a total of 6 doses. Subsequent intrathecal cytarabine may be administered at the discretion of the treating physician. Subjects who have persistent CNS disease despite 6 doses of intrathecal cytarabine will be off study treatment.

[β] See Appendix L - During the OEP, only AEs/SAEs, IP dispensing and accountability, concomitant medications/procedures, and SPMs will be monitored.

6. PROCEDURES

All procedures will be performed as outlined in the table of events (Table 2).

6.1. Screening, Study Entry and Treatment Procedures

Pediatric subjects from 1 to ≤ 18 years of age with rrAML will be considered for participation in this study. The subject(s) and/or guardian(s) (as appropriate by local law and regulations) will be provided with a written ICF or IAF, given the opportunity to ask any questions concerning the study and will sign an ICF or IAF prior to participating in any study procedures.

All subjects who sign an ICF/IAF or children of parents and/or guardians who sign the parental consent must be screened into the IWRS immediately upon signature.

After giving written informed consent/informed assent, subjects will undergo screening assessments to be assessed for study eligibility. Subjects who do not meet the eligibility criteria or who withdraw (for any reason) during the Screening Phase will be considered screen failures (sites should log onto the IWRS immediately to screen fail the subject in the system). Study-specific medical procedures to confirm eligibility are to be performed after signing ICF/IAF and must take place within 14 days prior to Cycle 1 Day 1.

Subjects who fail screening may be rescreened at any time, and as considered appropriate, at the Investigator's discretion. For subjects who are rescreened, a new ICF/IAF will need to be signed and screening procedures will need to be repeated if originally more than 14 days prior to the rescreen date.

6.2. Administration of Intrathecal Cytarabine

Intrathecal cytarabine (age-based dosing) will be administered prior to Cycle 1 in all subjects at the time of screening through lumbar puncture. Intrathecal cytarabine will be given within 2 weeks prior to administration of lenalidomide:

- For subjects without CNS involvement, subsequent intrathecal cytarabine may be administered at the discretion of the treating physician.
- For subjects with CNS involvement at screening, intrathecal cytarabine will be administered twice weekly x 4 doses and until CSF is clear on 2 consecutive evaluations for up to 6 total doses.
  - Subjects whose CSF was cleared may then receive subsequent intrathecal cytarabine doses at the discretion of the treating physician
  - Subjects who have persistent CNS disease despite 6 doses of intrathecal cytarabine will be off study treatment.

6.3. Demographics and Medical History

Demographics including gender, race, ethnicity, and date of birth (DOB) (where allowed by local regulations) will be documented at screening only. Race designations should include American Indian or Alaska native; Asian; Black or African American; Native Hawaiian or other Pacific

Islander; or White. For Ethnicity, designations will include Hispanic/Latino or Not Hispanic/Latino.

Relevant medical history for the past (up to 5 years) including current disease and the date of initial AML diagnosis will be recorded on the respective CRF at screening.

6.4. Prior Medications/Procedures

All prior medications/procedures (including chemotherapy, cytotoxic therapy, radiotherapy and HSCT) 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. All other prior medications/procedures used within 14 days of signing the ICF/IAF should also be recorded.

6.5. Confirmation of Disease Relapse

Disease diagnosis/relapse including morphology will be reviewed locally at screening from all subjects and retrospectively confirmed by a central reviewer using bone marrow aspirate slide (or bone marrow biopsy paraffin embedded slide) and peripheral blood smear slide. All dates of AML relapse or refractory status should be recorded, this should be at least 2 separate occurrences per study entry criteria. In the case where a study center has an IRB- and Celgene-approved procedural ICF/IAF that allows collection of additional bone marrow samples for potential research purposes, the latest pre-study PB and BM aspirate/biopsy may be used for screening study assessments.

Results from cytogenetics, FISH studies, flow cytometry studies, and molecular studies performed locally at initial diagnosis and/or relapse will be reported including FISH for t(16;16), t(8;21), MLL (11q23), t(15;17), monosomy 7, del(5q), or any other recurring abnormalities and presence or absence of mutations in Fms-like tyrosine kinase 3 (FLT3), or Nucleophosmin (NPM1), CCAAT/enhancer-binding protein alpha (CEBP-alpha). If exome sequencing has been performed by the local site (eg, Foundation Heme or other CLIA-approved clinical sequencing platform), the results will be reported.

6.6. 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, and at any unscheduled visits (only if clinically indicated).

6.7. Physical Examinations

All subjects will have a complete routine physical examination at screening, on Days 1, 8, 15, and 22 of Cycle 1, bi-weekly during Cycle 2, and on Day 1 of every cycle thereafter, at the Treatment Discontinuation Visit, on the 28-day Follow-up Visit, and at any unscheduled visits (only if clinically indicated).

6.8. Pregnancy Testing and Pregnancy Risk and Lenalidomide Counseling

Medically supervised serum pregnancy tests with a sensitivity of at least 25 mIU/mL must be conducted in FCCBP/FCBP, including those who commit to complete abstinence. FCCBP defined as a female who has achieved menarche and/or breast development in Tanner stage 2 or greater and has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries). FCBP defined as a sexually mature woman who has not undergone a hysterectomy or bilateral oophorectomy and has not been naturally postmenopausal for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months). FCCBP/FCBP must have 2 negative pregnancy tests (with sensitivity of at least 25 mIU/mL) prior to starting lenalidomide. The first pregnancy test in both FCCBP and FCBP must be performed within 10 – 14 days prior to the start of lenalidomide (Screening Phase) and the second pregnancy test must be performed within 24 hours prior to the start of lenalidomide (Cycle 1 Day 1).

NOTE: The pregnancy test 10 to 14 days prior to initiation of lenalidomide may be omitted, at the discretion of the investigator, for any FCCBP/FCBP who has high acuity disease requiring immediate treatment with lenalidomide. The pregnancy test within 24 hours prior to the first dose of lenalidomide is required to be performed.

Amenorrhea following cancer therapy does not rule out childbearing potential.

FCCBP/FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at Treatment Discontinuation Visit, and at Day 28 following IP discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study Treatment Discontinuation Visit, and at Days 14 and 28 following IP discontinuation.

Note: The subject may not receive lenalidomide until the Investigator has verified that the result of the pregnancy test performed on Day 1 of every cycle is negative. See inclusion criteria (Section 7.2) for pregnancy testing requirements.

At each visit, the Investigator must confirm with the FCCBP/FCBP that she is continuing to use 2 reliable methods of birth control if not committing to complete abstinence or plans not to commit to complete abstinence. Counseling about pregnancy precautions and the potential risks of fetal exposure to lenalidomide must be conducted at screening, on Day 1 of each cycle prior to lenalidomide dispensing and at a minimum of every 28 days, at the Treatment Discontinuation Visit, and at the 28-day Follow-up Visit. If pregnancy or a positive pregnancy test does occur in a study subject, lenalidomide must be immediately discontinued. Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. IP treatment must be discontinued during this evaluation. Female children and adult females must agree to abstain from breastfeeding during study participation and for at least 28 days after IP discontinuation. If pregnancy or a positive pregnancy test does occur in the partner of a male study subject during study participation, the Investigator must be notified immediately.

Any pregnancies that occur in (FCCBP/FCBP) subjects while the subject is in the Treatment Phase, or within 28 days thereafter, are considered immediately reportable events (see Section 11.4). Furthermore, FCCBP/FCBP and male subjects that have reached puberty must agree to undergo physician-approved reproductive education and discuss the side effects of lenalidomide on reproduction with parent(s) and/or guardian(s). Pregnancy testing is not required for non-FCCBP subjects, unless deemed necessary by the Investigator.

6.9. Performance Status

The performance status, depending on age, will be measured using the Karnofsky performance status score for subjects ≥ 16 years or Lansky performance status score for subjects < 16 years (Appendix E and Appendix F, respectively) at screening, on Day 1 of every cycle and at the Treatment Discontinuation Visit.

6.10. Echocardiography

An echocardiography will be performed at screening, at the end of Cycles 4 and 12 and at the Treatment Discontinuation Visit. If clinically indicated, echocardiography may be repeated during the study at the discretion of the Investigator.

6.11. Electrocardiogram

An electrocardiogram will be done at screening and at any unscheduled visits (only if clinically indicated).

6.12. Height and Weight

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 if weight changes by 10% or more during the Treatment Phase.

6.13. Chest X-ray

A chest X-ray is not needed if a previous chest X-ray taken within 4 weeks prior to Day 1 of Cycle 1 is available and not clinically significant, otherwise a chest X-ray will be performed at screening.

6.14. Laboratory Assessments

Laboratory testing will be performed locally at the study sites. It is the responsibility of the Investigator to assess the clinical significance of all abnormal values as defined by the reference ranges from the laboratory. Requirements for reporting laboratory abnormalities as AEs can be found in Section 11.3. Laboratory parameters outside the normal range, which are judged by the Investigator to be clinically significant (eg, those which require concomitant therapy or procedures, changes in study treatment or further diagnostic measures) will be recorded as AEs in the CRF. This does not hold true if the laboratory abnormality in the view of the Investigator is caused by the underlying disease. Clinically significant laboratory abnormalities at screening may result in a subject being ineligible for the study and should not be captured as an AE. Any abnormal values that persist should be followed at the discretion of the Investigator. The

Investigator should file all copies of the local laboratory reports including faxes with the subject's medical chart.

6.14.1. Hematology Laboratory Assessments

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 (if clinically indicated). White blood cell count, absolute neutrophil count, absolute blast count, and platelet count will be recorded in the CRF, all other hematology laboratory values will not be collected on a laboratory CRF; instead, laboratory abnormalities that are considered AEs should be reported as AEs on the AE CRF (see Section 11). Whenever a hematology sample is collected for a complete blood count (CBC), a peripheral blood smear will be used to assess a manual blood count differential.

6.14.2. 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 (if clinically indicated). Serum chemistry laboratory values will not be collected on a laboratory CRF; instead, laboratory abnormalities that are considered AEs should be reported on the AE CRF (see Section 11).

6.14.3. Urinalysis (dipstick)

Urinalysis will include at a minimum specific gravity, pH, glucose, protein, ketones, blood, leukocyte esterase and nitrites, and will be performed at screening and at unscheduled visits (if clinically indicated). A microscopic examination (including casts, RBCs, and WBCs) should be performed in the event of a positive result for (at a minimum): blood, leukocyte esterase, or nitrites.

6.15. Concomitant Medications/Procedures

All subjects will have concomitant medications and procedures recorded from the time of signing the ICF/IAF until the 28-day Follow-up Visit. A complete list of all medications (prescription, over the counter, nutritional, fiber supplements, etc.), dose, dosing regimen, and start and stop dates used prior to and during the study will be recorded on the CRF. Refer to Section 9 for a listing of permitted and prohibited concomitant medications.

6.16. IP Administration

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

Females of child bearing potential (FCBP) should not handle or administer lenalidomide unless they are wearing gloves. All subjects should not extensively handle the lenalidomide capsules or oral suspension. The lenalidomide capsules should not be broken, chewed, or opened and should be maintained in the packaging until ingestion. Refer to the subject diary and the manual on preparation, administration, and handling of the lenalidomide oral suspension for specific details.

In investigational studies, lenalidomide will be dispensed through a qualified healthcare professional (including but not limited to, nurses, pharmacists and physicians). These healthcare professionals will be trained by Celgene in requirements specific to counseling of subjects. Once trained, these healthcare staff will counsel subjects prior to lenalidomide being dispensed to ensure that the subject has complied with all requirements (including use of birth control and pregnancy testing for FCBP) and that the subject understands the risks associated with lenalidomide. This step will be documented with a completed Education and Counseling Guidance Document and no lenalidomide will be dispensed until this step occurs. Counseling includes verification with the subject that required pregnancy testing was performed and results were negative.

A Lenalidomide Information Sheet will be supplied each time lenalidomide is dispensed.

6.17. IP Dispensing

Lenalidomide should be dispensed on Day 1 of every cycle including the OEP. Only enough lenalidomide for 1 cycle of therapy will be dispensed with each cycle of therapy. The first dose of lenalidomide will be administered at the study center after the completion of all clinical procedures required for Cycle 1 Day 1 with the exception of the collection of PK sampling. When multiple capsules are required to make up the accurate daily dosage, detailed instructions will be provided to the subject to ensure accurate dosages are taken (Appendix B).

Refer to Appendix C for dosing guidelines for the lenalidomide oral suspension.

Detailed instructions on preparation, administration, and handling of the lenalidomide oral suspension will be provided in a separate manual.

6.18. IP Accountability

All IP that is dispensed during the course of the study will be reconciled and accounted for by the Investigator (or designee). Applicable information such as lot number, date dispensed, numbers of capsules or vials dispensed, date returned, the number of capsules returned, or number of vials returned should be collected as well as information provided by the subject or the caregiver (eg, subject dosing diary). IP accountability should be completed on Cycle 1 Day 1, at the end of every treatment cycle (eg, on Day 1 of Cycle 2, Day 1 of Cycle 3), at the end of every cycle in the OEP if treatment continues beyond 12 cycles, and at the Treatment Discontinuation Visit.

6.19. Information to be Collected on Screen Failures

The informed consent date, demographics, reason subject did not qualify for the study and the Investigator's signature will be collected for all subjects determined to be screen failures. If the reason for the screen failure is an AE, the AE and concomitant medications used to treat the AE will be recorded on the CRF and captured in the subject's source documents from the date of signing informed consent to the day the subject is confirmed to be a screen failure. Relevant information will also be recorded on the Screening Log.

6.20. Treatment Activity

The primary endpoint consists of the assessment of the morphologic complete response rate within the first 4 cycles of study treatment with lenalidomide. Morphological complete response is defined as CR or CRi. These response criteria will be determined using the revised AML IWG criteria (Cheson, 2003) (Appendix D).

6.20.1. Bone Marrow Aspirate or Biopsy and Peripheral Blood

To determine morphologic CR/CRi, BMA/biopsy and peripheral blood smear must be collected from all subjects at screening and at the completion of the 21-day treatment period of the predefined treatment Cycles 1, 2, 3 and 4 within 6 days **before dosing for each subsequent cycle** (ie, between Day 22 to Day 27 of that cycle) (Table 2). If morphologic CR/CRi is achieved within the first 2 cycles, BMA/biopsy and peripheral blood smear will not be required at the end of Cycle 3. For all subjects, BMA/biopsy and peripheral blood smear must be performed at the completion of Cycle 4, and at the Treatment Discontinuation Visit or at the time of suspected relapse (whichever occurs first). For subjects who are assessed as having partial response, the BMA/biopsy and peripheral blood smear will be repeated at Cycle 8 unless the subject goes to allogeneic HSCT, and at the Treatment Discontinuation Visit or at the time of suspected treatment failure (whichever occurs first). ***A bone marrow biopsy is required only if a bone marrow aspirate cannot be obtained***. Subjects demonstrating clinical benefit as per the Investigator at the end of Cycle 4 and beyond may continue to receive lenalidomide on study for up to 12 cycles in the absence of protocol-defined toxicity or transitioning to allogeneic HSCT.

In the case where a study center has an IRB- and Celgene-approved procedural ICF/IAF that allows collection of additional bone marrow samples for potential research purposes, the latest pre-study PB and BM aspirate/biopsy may be used for screening study assessments.

The screening BMA slide (and/or bone marrow biopsy paraffin embedded slide) and peripheral blood smear slide **must** be provided to the central reviewers at . The central review will provide standardized analysis and reporting for all subjects. The central reviewer's assessment will be used retrospectively to confirm diagnosis.

In addition, BMA/biopsy will be obtained to confirm CR, CRi, partial remission (PR), or treatment failure, as assessed by the Investigator based on complete blood count [CBC] with white blood cell (WBC) differential results (defined in Appendix D). Morphological response will be assessed based on peripheral blood count recovery and morphologic assessment of

BMAs/biopsies (Table 2). Assessments to be collected during the Follow-up Phase will include new anticancer therapies, HSCT, SPMs, SAEs, .

For screening assessments, instructions for submission of pathology data (flow cytometry, reports of cytogenetics and FISH) to , central reviewer, are provided in Appendix I.

6.20.3. Cytogenetics/FISH

A bone marrow aspirate sample for cytogenetics testing/chromosome analysis/FISH testing for prior positive markers will be obtained to analyze karyotype at screening and whenever a BMA/biopsy is obtained at the completion of the 21-day treatment period of treatment cycles within 6 days **before dosing for each subsequent cycle** (ie, between Day 22 to Day 27 of that cycle), and at the Treatment Discontinuation Visit or at the time of suspected relapse (whichever occurs first).

During the study, a repeat of local testing of bone marrow cytogenetics and FISH for any positive markers is to be completed whenever a BMA/biopsy is obtained. However, if the cytogenetics/FISH results are '**normal**' at screening or at any point during the study, cytogenetic analysis is not required to be repeated except at the Treatment Discontinuation Visit or at the time of bone marrow evaluation for suspected relapse (whichever occurs first).

For the screening assessment, the cytogenetic files **must** be provided to the central reviewers at . The central review will provide standardized analysis and reporting for all subjects. Instructions for submission of cytogenetics files to , central reviewer, are provided in Appendix I.

6.20.4. Modified IWG Response

Modified International Working Group response (Appendix D) criteria will be used to assess activity at the completion of predefined treatment Cycles 1, 2, 3 and 4 and at the Treatment Discontinuation Visit or at the time of suspected relapse (whichever occurs first). An IWG response assessment will be performed whenever a bone marrow assessment is performed in order to confirm CR or CRi, PR, or treatment failure. For subjects who are assessed as having partial response, the IWG response will be repeated at Cycle 8 unless the subject goes to allogeneic HSCT, and at the Treatment Discontinuation Visit or at the time of suspected treatment failure (whichever occurs first).

6.21. Safety

Safety assessments will consist of evaluating AEs, SAEs and concomitant medications/therapies used to treat them. Safety assessments may include monitoring of any or all of the following parameters: subject's clinical symptoms, physical examination findings, laboratory assessment of hematology and serum chemistry parameters, vital signs, performance status, ECG, echocardiogram, urinalysis, or pregnancy testing for FCCBP/FCBP, pathological, radiological or surgical findings, or other appropriate tests and procedures.

6.21.1. Adverse Events Reporting

All AEs will be recorded by the Investigator from the time the informed consent/assent signing until 28 days after the last dose of lenalidomide, as well as those SAEs made known to the Investigator at any time thereafter that are suspected of being related to lenalidomide. Adverse events, including second malignancies and cardiovascular events, will be monitored and reported throughout the reporting period as AEs/SAEs as applicable. Adverse events and SAEs will be recorded on the AE page of the CRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. For additional details see Section 11.

6.21.2. Second Primary Malignancies

Second primary malignancies (SPMs) will be monitored as events of interest and should be included as part of the assessment of AEs throughout the course of the study. Investigators are to report any SPM as SAEs regardless of causal relationship to lenalidomide, occurring at any time for the duration of the study, from the time of signing the ICF/IAF until all subjects have been followed for up to 5 years from the last subject's first dose, unless consent is withdrawn, the subject is lost to follow-up or dies. Events of SPM are to be reported using the SAE report form and must be considered an "Important Medical Event" even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the CRF and subject's source documents. Documentation on the diagnosis of the SPM must be provided at the time of reporting as a SAE (eg, any confirmatory histology or cytology results, X-rays, computed tomography [CT] scans, etc.).

Information about common side effects already known about lenalidomide will be included in the subject informed consent form and should be discussed with the subject as needed during the study. This information can also be found in the Investigator's Brochure (IB) or will be communicated between IB updates in the form of Investigator notifications.

6.22. Treatment Discontinuation

All discontinued subjects, regardless of reason for discontinuation, should undergo treatment discontinuation procedures at the time of IP discontinuation. The treatment discontinuation procedures include physical examination, vital signs, echocardiogram, performance status, hematology, serum blood chemistry, pregnancy testing for FCCBP/FCBP, lenalidomide counseling, collections of AEs, concomitant medications and procedures, IP administration recording, and IP accountability. Bone marrow aspirate/biopsy, peripheral blood smear, cytogenetic testing, and IWG response assessment will be measured. If clinically inappropriate per the treating site, the subject may have bone marrow evaluation omitted if peripheral blast results are collected. The reason for discontinuation will also be documented in the CRF and in the source document.

6.23. Follow-up Phase

Subjects will enter the Follow-up Phase at the time of permanent discontinuation of 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.

A 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, physical examination (including vital signs), hematology, serum blood chemistry, lenalidomide counseling, SPMs, and anticancer therapies. Female Children of Childbearing Potential and FCBP will have a pregnancy test at the 28-day Follow-up Visit (see Section 6.8 and Section 7.2).

After the 28-day Follow-up Visit, subjects will be followed-up long term 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.

6.24. 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 (see Section 12) may enter the optional extension phase (OEP). Details for OEP are provided in Appendix L.

6.25. Investigational Product Specific Safety Concerns To Be Monitored or Assessed

Embryo-Fetal Exposure and PregnancyWarning: Lenalidomide is a chemical analog of thalidomide structurally related to thalidomide. Thalidomide is a known human teratogen that causes severe life-threatening birth defects. Lenalidomide induced malformations in monkeys similar to those described with thalidomide. If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans cannot be ruled out. Sexually mature subjects will be required to adhere to the Celgene approved pregnancy prevention program. Additionally, all

subjects and/or parents/guardians will be required to have an understanding that lenalidomide could have a potential teratogenic risk. All FCCBP/FCBP and male subjects will be counseled about pregnancy precautions and risks of fetal exposure according to the REVLIMID REMS (Risk Evaluation and Mitigation Strategies) program (Lenalidomide IB).

Adverse Events of Specific Concern: Adverse events of specific concerns associated with the administration of lenalidomide observed in adults in marketed indications include:

- *Hematologic toxicity*: Lenalidomide is associated with significant neutropenia and thrombocytopenia. Subjects may require dose interruption and/or dose reduction.
- *Deep vein thrombosis and pulmonary embolism*: Physicians and subjects should be observant for signs and symptoms of thromboembolism. Subjects with a history of non-catheter associated thromboembolic events or with a known genetic predisposition to thrombophilia (ie, Factor V Leiden mutation) will receive prophylactic anticoagulation with low-molecular-weight heparin (LMWH), or other appropriate medication. All other subjects enrolled on study will be considered for prophylactic antithrombotic treatment in accordance with local treatment practices, current treatment guidelines, treating physician discretion, and a careful risk-benefit assessment. Should prophylactic anticoagulation be instituted, the platelet count will be maintained greater than 50,000 with platelets transfusions as needed. If the platelet count cannot be maintained > 50,000 with transfusions, the Investigator should interrupt anticoagulation.
- *Allergic reactions*: Allergic reactions associated with lenalidomide include hypersensitivity, angioedema, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN). In some cases, these allergic reactions may be fatal. Lenalidomide will be discontinued if any such reactions are suspected. Lenalidomide will not be resumed following discontinuation for these reactions.
- *Hepatotoxicity*: Hepatic failure, include fatal cases, has occurred in patients treated with lenalidomide in combination with dexamethasone. The mechanism of drug-induced hepatotoxicity is unknown. Pre-existing viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors. Monitor liver enzymes periodically. Stop lenalidomide upon elevation of significantly elevated liver enzymes. After return to baseline values, treatment at a lower dose may be considered.
- *Lenalidomide capsules contain lactose*. The risk-benefit of lenalidomide treatment will be evaluated in subjects with lactose intolerance.
- *Tumor lysis syndrome (TLS)*: Fatal instances of TLS have been reported during treatment with lenalidomide. Subjects at risk for TLS (ie, those with high tumor burden) will be closely monitored for development of TLS with the initiation of lenalidomide.
- *Tumor flare reaction (TFR)*: Serious tumor flare reactions have occurred during investigational use of lenalidomide for CLL and lymphoma. Although TFR has not been reported in adult AML, patients at risk of TLS (ie, those with high tumor burden) will be closely monitored for development of TFR.

- *Increased mortality due to cardiac events*: Serious and fatal cardiac adverse reactions were observed in patients with CLL. Please refer to the REVLIMID US prescribing information (REVLIMID USPI) for further information. Appropriate monitoring measures for cardiac toxicity are implemented in the protocol.
- *Second primary malignancy (SPM)*: Higher incidences of SPM were observed in controlled trials of patients with MM receiving lenalidomide. All subjects will be followed for SPM for 5 years from the last subject's first dose of IP, until withdrawal of consent, lost to follow-up or death.
- *Graft-versus-host disease (GVHD):* GVHD was observed in adult IIT trials investigating lenalidomide as maintenance therapy in patients following allogeneic HSCT in remission (Kneppers, 2011; Sockel, 2011), and in relapsed MM and relapsed AML patients previously treated with allogeneic HSCT who responded to lenalidomide (Ades, 2010; Bensinger, 2012; El-Cheikh, 2012; Ford, 2010; Lioznov, 2010; Montefusco, 2012). Additionally, GVHD rash has been reported in relapsed adult AML/MDS and MM patients after achieving CR with lenalidomide post allogeneic stem cell transplantation HSCT (Blum, 2010; Ford, 2010). Subjects in this study will be closely monitored for GVHD and specific GVHD stopping criteria have been developed. For additional details see Section 8.2.1.

6.26. Pharmacokinetic Sample Collection

6.26.1. 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 3) for 24 hours postdose. The actual date and time for dosing and blood sampling should be recorded in CRF.

As food may affect the absorption of lenalidomide, subjects will be asked to fast at least 2 hours prior to dosing and 2 hours after dosing of lenalidomide on Day 1 in order to reduce variability in PK results. Approximately 1 mL of blood will be drawn for each PK sample. Specific details regarding the collection, handling, processing, storage, and shipment of PK samples (blood) can be found in Appendix H.

Table 3: 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.

Subjects should return to the clinic on Day 2 for the 24-hour postdose PK sample, which should be taken prior to lenalidomide administration. However, at the discretion of the Investigator and for convenience of the subject, the subject can be hospitalized overnight at the clinic from Day 1 to Day 2 of Cycle 1 to facilitate collection of the 24-hour postdose sample.

7. STUDY POPULATION

7.1. Number of Subjects and Sites

The study will enroll pediatric subjects from 1 to ≤ 18 years of age at the time of screening with rrAML with at least 2 prior induction therapy attempts. A total of up to 43 evaluable subjects (18 in Stage 1 and an additional 25 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 70 sites. Approximately 50% of enrolled subjects will be younger than 12 years of age to provide adequate PK data for this age subset. The study will be conducted initially in North America (United States of America and Canada) and may be expanded globally.

7.2. Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study:

1. Male or female is 1 to ≤ 18 years of age at the time of signing the ICF/IAF.
2. Subject (when applicable, parental/legal representative) must understand and voluntarily provide permission to the ICF/IAF prior to conducting any study-related assessments/procedures.
3. Subject has rrAML after at least 2 prior induction attempts:
   - Bone marrow aspirate or biopsy must have ≥ 5% blasts by morphology and/or flow cytometry.
   - Each block of chemotherapy (ie, ADE, MA) is a separate reinduction attempt.
   - Donor lymphocyte infusion (DLI) is considered a reinduction attempt.
4. Subject is willing and able to adhere to the study visit schedule and other protocol requirements.
5. Subject has a Karnofsky score of ≥ 50% (subjects ≥ 16 years of age) or a Lansky score ≥ 50% (subjects < 16 years of age).
6. Subject has a resting left ventricular ejection fraction (LVEF) of ≥ 40% obtained by echocardiography.
7. Subject has recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to first dose. All prior treatment-related toxicities must have resolved to ≤ Grade 2 prior to enrollment.
8. Regarding radiation therapy, time elapsed prior to first dose of lenalidomide:
   - 2 weeks for local palliative radiation therapy (XRT).
   - 8 weeks if prior craniospinal chemoradiation therapy (CRT) or if ≥ 50% radiation of pelvis.
   - 6 weeks if other bone marrow radiation has been administered.

9. Graft-versus-host disease criteria:
   - Subject must be at least 2 months (from first dose of lenalidomide) from stem cell infusion.
   - Subject must have no evidence of active acute or chronic GVHD (Grade 0) for 4 weeks prior to the first dose of lenalidomide.
     - If the subject has a history of maximum Grade 1 or 2 GVHD that was treated with systemic steroid (≥ 0.5 mg/kg/day prednisone equivalents) or other non-steroid systemic IST, the subject must be off all IST for at least 2 weeks, and must have ceased treatment doses of steroids for GVHD (≥ 0.5 mg/kg/day prednisone equivalents) for at least 4 weeks.
     - If the subject has a history of Grade 3 or greater GVHD, the subject must be off all systemic IST for 4 weeks.
     - Topical therapy is permitted and does not imply the subject has active acute or chronic GVHD.
   - Physiologic dosing of hydrocortisone is permitted.
10. At least 4 weeks (from first dose) elapsed from donor lymphocyte infusion (DLI) without conditioning.
11. Subject has adequate renal function, which is defined as:
    - Creatinine clearance calculated (Table 4) using the Schwartz formula, (Schwartz, 1976) or radioisotope glomerular filtration rate (GFR) > 70 mL/min/1.73 m^2.

Table 4: Creatinine Clearance Estimation using the Schwartz Formula

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 month to < 6 months	0.4	0.4
6 months to < 1 year	0.5	0.5
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1.0	1.0
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this table were derived from the Schwartz formula for estimating glomerular filtration rate (GFR) (Schwartz, 1976) utilizing child length and stature data published by the Center for Disease Control (CDC).

12. Subject has adequate liver function, which is defined as:
    - Total bilirubin is ≤ 2 mg/dL unless the increase in bilirubin is attributable to Gilbert's Syndrome

- AST is ≤ 3.0 x upper normal limit (ULN) for age. For the purpose of this study, the ULN for AST is 50 U/L.
- ALT is ≤ 3.0 x upper normal limit (ULN) for age. For the purpose of this study, the ULN for ALT is 45 U/L.

13. Female Children of Childbearing Potential, Female of Childbearing Potential and male subjects that have reached puberty must agree to undergo physician-approved reproductive education and discuss the side effects of the study therapy on reproduction with parent(s) and/or guardian(s).
14. All subjects and/or parents/guardians must have an understanding that lenalidomide could have a potential teratogenic risk. Female Children of Childbearing Potential, defined as females who have achieved menarche and/or breast development in Tanner Stage 2 or greater and have not undergone a hysterectomy or bilateral oophorectomy and FCBP defined as a sexually mature woman who has not undergone a hysterectomy or bilateral oophorectomy and has not been naturally postmenopausal for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months) must meet the following conditions below (Note: Amenorrhea following cancer therapy does not rule out childbearing potential):

    - Medically supervised serum pregnancy tests with a sensitivity of at least 25 mIU/mL must be conducted in FCCBP/FCBP, including those who commit to complete abstinence*. FCCBP/FCBP must have two pregnancy tests (with a minimum sensitivity of 25 mIU/mL) prior to starting treatment with lenalidomide. The first pregnancy test must be performed within 10 – 14 days prior to the start of lenalidomide treatment and the second pregnancy test must be performed within 24 hours prior to starting treatment with lenalidomide.

      NOTE: The pregnancy test 10 to 14 days prior to initiation of lenalidomide may be omitted, at the discretion of the investigator, for any FCCBP/FCBP who has high acuity disease requiring immediate treatment with lenalidomide. The pregnancy test within 24 hours prior to the first dose of lenalidomide is required to be performed.

      The subject may not receive IP until the Investigator has verified that the results of these pregnancy tests performed on Cycle 1 Day 1 are negative. FCCBP/FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study Treatment Discontinuation Visit, and at Day 28 following IP discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study Treatment Discontinuation Visit, and at Days 14 and 28 following IP discontinuation.
    - Female subjects must, as appropriate to age and at the discretion of the study Investigator, either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis) and/or agree to the use of two reliable forms of approved and effective contraceptive methods simultaneously. The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method (oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or

vasectomized partner) without interruption, 28 days prior to starting lenalidomide treatment, throughout the entire duration of study treatment including dose interruptions and 28 days after the end of study treatment.

- All male and female subjects must follow all requirements defined in the Pregnancy Prevention Program.

15. Male subjects, as appropriate to age and the discretion of the study physician:
    - Must practice true abstinence* or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 28 days following lenalidomide discontinuation, even if he has undergone a successful vasectomy or practices complete abstinence.

7.3. Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

1. Subject has Down syndrome.
2. Subject has French-American-British classification (FAB) type M3 leukemia (acute promyelocytic leukemia) or identification of t(15;17).
3. Subject has isolated CNS involvement or extramedullary relapse. (Subjects with combined CNS/marrow relapse may be enrolled).
4. Subject has had prior treatment with cytotoxic chemotherapy within 2 weeks of the first dose of lenalidomide with the exception of hydroxyurea (allowed prior to the first dose of lenalidomide and through Day 14 of Cycle 1) and intrathecal (IT) cytarabine will be administered within 2 weeks prior to administration of lenalidomide.
5. Subject has had prior treatment with biologic antineoplastic agents less than 7 days before the first dose of lenalidomide. For agents that have known AEs occurring beyond 7 days after administration (ie, monoclonal antibodies), this period must be extended beyond the time during which acute AEs are known to occur.
6. Subject has had prior treatment with lenalidomide.
7. Subject is pregnant or lactating.
8. Subject has an uncontrolled systemic fungal, bacterial, or viral infection (defined as ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics, antiviral therapy, and/or other treatment).
9. Subject has known Human Immunodeficiency Virus (HIV) positivity (subjects who are receiving antiretroviral therapy for HIV disease).
10. Subject has a prior history of malignancies other than AML unless the subject has been free of the disease for ≥ 5 years from first dose of lenalidomide.
11. The presence of any of the following will exclude a subject from enrollment:
    - Subject has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.

- Subject has any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study.
- Subject has any condition that confounds the ability to interpret data from the study.

12. Subject has cardiac disorders (Common Terminology Criteria for Adverse Events [CTCAE] version 4.03 Grade 3 or 4).
13. Subject has a history of well-documented prior veno-occlusive disease (VOD).
14. Subject has any other organ dysfunction (CTCAE version 4.03 Grade 4) that will interfere with the administration of the therapy according to this protocol.

7.4. Inclusion and Exclusion Criteria for OEP

Refer to Appendix L – Optional Extension Phase.

Note: *True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception].

8. DESCRIPTION OF STUDY TREATMENTS

8.1. Description of Investigational Product(s)

Investigational product will be provided as capsule formulation and as active pharmaceutical ingredient (API) in vials for constitution to oral suspension.

Celgene Corporation will supply lenalidomide 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg and 25 mg capsules as hard gelatin capsules for oral administration. The 2.5 mg dose is contained in a size 4 hard gelatin capsule. The 5 mg dose is contained in a size 2 hard gelatin capsule. The 10 mg, 15 mg, 20 mg and 25 mg doses are contained in a size 0 hard gelatin capsule. Lenalidomide capsules should be swallowed whole and should not be broken, chewed or opened. Each dosage will be provided in 21 count bottles.

Celgene Corporation will supply lenalidomide API in individual sealed vials for constitution to oral suspension. Each vial contains 80 mg of lenalidomide with no inactive ingredients. The lenalidomide powder in each vial is constituted with 8 ml of suspending agent to create a lenalidomide suspension with a final concentration of 10 mg/ml. This suspension is intended for oral administration only.

Females of child bearing potential (FCBP) should not handle or administer lenalidomide unless they are wearing gloves. All subjects should not extensively handle the lenalidomide capsules or oral suspension. The lenalidomide capsules should not be broken, chewed, or opened and should be maintained in the packaging until ingestion. Refer to the subject diary and the manual on preparation, administration, and handling of the lenalidomide oral suspension for specific details.

If a subject is receiving lenalidomide oral suspension, a home healthcare company can be available to assist with the preparation and administration of the oral suspension at the subject's home. The home trial support agent that may visit the subject's home would be a licensed nurse. Refer to the manual on preparation, administration, and handling of the lenalidomide oral suspension for specific details.

In investigational studies, lenalidomide will be dispensed through a qualified healthcare professional (including but not limited to nurses, pharmacists and physicians). These healthcare professionals will be trained by Celgene in requirements specific to counseling of subjects. Once trained, these healthcare staff will counsel subjects prior to lenalidomide being dispensed to ensure that the subject has complied with all requirements (including use of birth control and pregnancy testing for FCBP) and that the subject understands the risks associated with lenalidomide. This step will be documented with a completed Education and Counseling Guidance Document and no lenalidomide will be dispensed until this step occurs. Counseling includes verification with the subject that required pregnancy testing was performed and results were negative.

A Lenalidomide Information Sheet will be supplied each time lenalidomide is dispensed.

8.2. Treatment Administration and Schedule

Lenalidomide will be administered either in capsules containing 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg or 25 mg or as an oral suspension (10 mg/mL). The oral suspension is available for use in

subjects who are unable to swallow the capsules or at the discretion of the investigator. The starting dose of lenalidomide will be 2 mg/kg/day with a maximum dose of 70 mg/day. Lenalidomide will be administered orally once daily for the first 21 days of every 28-day cycle. Daily dosage should be administered using the combinations that yield the least amount of capsules. However, if a subject is unable to swallow big capsules, varying, appropriate strength combinations may be considered during medication assignment using the IWRS. The prescribed dose should be the closest dose that can be given to the calculated dose based on the strengths of lenalidomide available. If the calculated dose falls between two integers, the dose calculated should be rounded up or down to the nearest whole number. The actual dose to be administered can be determined after rounding the calculated dose. For dose reductions, the dose calculated should be to the nearest whole number. For a dosing table with guidelines reflecting this approach for the lenalidomide capsules, refer to Appendix B.

Refer to Appendix C for dosing guidelines for the lenalidomide oral suspension.

After completion of 12 cycles of study treatment, if deemed necessary or useful by the Investigator and with approval of the Sponsor, subjects who demonstrate clinical benefit as per the Investigator from lenalidomide may continue to receive oral lenalidomide (either capsules or oral suspension) in an OEP until they meet the criteria for study discontinuation (see Section 12).

Dose interruptions/reductions will be permitted for episodes of myelosuppression, non-hematologic toxicities, and AEs. For additional details see Section 8.2.1.

In the event of 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) during the study. The dose will not be re-escalated once it has been reduced (Table 6). 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.

As per routine standard of care, intrathecal cytarabine (age-based dosing) will be administered prior to Cycle 1 in all subjects at the time of screening through lumbar puncture (Table 5). Intrathecal cytarabine will be administered within 2 weeks prior to administration of lenalidomide:

- For subjects without CNS involvement, subsequent intrathecal cytarabine may be administered at the discretion of the treating physician.
- For subjects with CNS involvement at screening, intrathecal cytarabine will be administered twice weekly x 4 doses and until CSF is clear on 2 consecutive evaluations for up to 6 total doses.
  - Subjects whose CSF was cleared may receive subsequent intrathecal cytarabine doses at the discretion of the treating physician.
  - Subjects who have persistent CNS disease despite 6 doses of intrathecal cytarabine will be off study treatment.

Table 5: Age-based Cytarabine Dosing

Age (years)	Dose
0 – 0.99	20 mg
1 – 1.99	30 mg
2 – 2.99	50 mg
≥ 3	70 mg

8.2.1. Dose Reductions/Interruptions

Dose reduction guidelines are as follows:

- Two dose reductions will be allowed (Table 6) 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 6: 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)

Definition of Toxicity Requiring Treatment Interruption and/or Dose De-escalation

Lenalidomide dosing will be interrupted for any of the following toxicities at least possibly attributed to lenalidomide:

- Any Grade 4 non-hematological toxicity *with the specific exclusion* of fever or infection.
- Any Grade 3 non-hematological toxicity *with the specific exclusion* of:
  - Grade 3 nausea and vomiting controlled by antiemetics.

- Grade 3 fever or infection.
- Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to oral supplementation.
- Grade 3 TLS: With close monitoring per the TLS monitoring guidelines (Appendix M Tumor Lysis Syndrome), lenalidomide dose may be continued uninterrupted provided continued treatment does not pose a safety concern in the presence of TLS event. If interrupted, lenalidomide treatment may be restarted at the same dose level after TLS is under control at the discretion of the Investigator.

NOTE: For purposes of grading AST and ALT adverse events in this study, the ULN for AST is 50 U/L and the ULN for ALT is 45 U/L.

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 TEN or Stevens-Johnson syndrome will not be retreated with lenalidomide.

Grade 3 ALT/AST values that return to levels that meet initial eligibility criteria within 7 days of IP interruption do not require a dose reduction. These subjects may resume treatment at the original dose level. If the toxicity recurs, then dose de-escalation is indicated.

Day 1 of Cycle 2 and beyond may be delayed up to 14 days from the end of the prior cycle in order for subjects to recover from toxicity. If a study interruption has lasted for more than 14 days, the Investigator should contact the Medical Monitor to discuss whether the subject should be continued on the study.

Special Instructions for Myelosuppression:

Due to the underlying marrow infiltrating malignancy, myelosuppression is universal and expected in patients with AML. Therefore, myelosuppression (anemia, neutropenia, and thrombocytopenia) will not require dose reduction or interruption *except* in the case of neutropenia or thrombocytopenia due to prolonged bone marrow aplasia at the end of a treatment cycle in subjects who have achieved remission.

- For subjects who have achieved remission:
  - Prolonged bone marrow aplasia is defined as lack of peripheral blood count recovery to ANC $\geq 500/mm^3$ and platelets $\geq 50{,}000/mL$ without transfusion for 7 days in the absence of leukemia (bone marrow biopsy demonstrate hypocellularity without evidence of leukemia) at Day 43 of a cycle (ie, failure to start the next cycle within 14 days).
  - The lenalidomide dose will be interrupted and the start of the next cycle will be delayed until count recovery.
  - Prolonged delay (ie, failure to start the next cycle within 14 days) for subjects in remission will require dose de-escalation.
  - If the peripheral blood counts recover within 14 days, the subject will proceed to the next cycle without dose reduction.

- If the peripheral blood counts do not recover within 14 days, repeat bone marrow evaluation including bone marrow biopsy every 7-14 days to assess cellularity and to evaluate for relapse/persistent leukemia.

- For subjects who have not achieved remission:
  - In general, subjects who have not achieved remission and have evidence of residual leukemia will proceed to the next cycle as scheduled regardless of count recovery.
- For subjects with residual leukemia:
  - If residual leukemia is demonstrated and the subject previously had achieved CR/CRi, the subject will be discontinued from the study.
  - If residual leukemia is demonstrated, which is stable from prior assessments (ie, subject with previous PR/treatment failure), the subject will proceed to the next cycle of lenalidomide as scheduled without delay and without regard to peripheral blood counts. Lenalidomide dose will NOT be decreased.

Special Instructions for Management of Graft Versus Host Disease (GVHD):

Post-HSCT subjects will be monitored closely for development of GVHD of the skin, liver, or gut, see Appendix K for grading criteria.

- Subjects with Grade 1 or 2 GVHD (any site, biopsy proven or probable, ie, requires systemic steroid treatment) will be managed at the discretion of the local bone marrow transplant (BMT) physician and lenalidomide will be held.
  - If the acute GVHD resolves within 14 days and the subject is being treated with no more than topical therapies and/or up to 0.5 mg/kg/day corticosteroids (prednisone equivalents), lenalidomide will be restarted at the same prior dose.
  - After 14 days, subjects requiring more than 0.5 mg/kg/day corticosteroids or other systemic therapy (ie, not including topical therapies) to manage the acute GVHD will be discontinued from the study.
- Subjects with Grade 3 or 4 GVHD (any site, suspected or biopsy proven) will have lenalidomide discontinued permanently and will be managed at the discretion of the local HSCT physician. These subjects will be discontinued from the study.

Guidelines for Renal Insufficiency

- Lenalidomide is primarily excreted unchanged by the kidney; therefore, study treatment will be held for subjects who experience CLcr < 70 mL/min (confirmed by repeat creatinine measurement within 3 days). If CLcr returns to levels that meet initial eligibility criteria (> 70 mL/min) within 7 days of IP interruption, the subject may resume treatment at a full dose. However, if the subject improves within 14 days, a dose reduction by 1 dose level of study treatment will be considered at the discretion of the Investigator, and after careful consideration of the subject's renal impairment etiology and the subject's tolerability to lenalidomide. If toxicity does not resolve to eligibility by 14 days of dose interruption, then the subject will be off study treatment.

Dose Discontinuation:

- Subjects experiencing a thromboembolic event unrelated to a central line will be discontinued from lenalidomide treatment.
- As described above, under dose interruption, any subject with evidence of TEN or Stevens-Johnson syndrome will not be retreated with lenalidomide.
- Subjects who do not tolerate 1 mg/kg/day will discontinue lenalidomide treatment.
- Subjects with non-hematologic toxicities that do not resolve to less than or equal to Grade 1 or baseline levels within 14 days will be off study treatment.
- Subjects with prolonged renal impairment (CLcr < 70 mL/min) lasting more than 14 days will be off study treatment.
- Subjects who do not demonstrate clinical benefit as per the Investigator at the end of Cycle 4 and beyond will be discontinued from lenalidomide treatment.

8.2.2. Overdose

Overdose, as defined for this 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 drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the CRF. See Section 11 for the reporting of AEs associated with overdose.

8.3. Method of Treatment Assignment

All subjects will be enrolled into the study using an IWRS. The Investigator or designated site staff will be assigned password protected, coded identification numbers that give them authorization to log into the IWRS. At screening, the Investigator or designated staff will log into the IWRS and provide the requested identifying information for the subject. The IWRS will then confirm the assignment of a 2-part unique subject number. The first part is the center number and the second part is one of a series of numbers allocated to subjects at that center. Once assigned to a subject, the subject number will not be reused. If the subject is not enrolled into the study the IWRS must be notified.

Prior to enrolling a subject, written ICF/IAF must be obtained, all screening evaluations must be completed, and eligibility criteria must be verified by the Sponsor. Once these actions have been completed, the Investigator or designated staff will log into the IWRS and confirm that the subject fulfills all the inclusion and exclusion criteria. The IWRS will assign an enrollment number to the subject which will be used to identify the subject in the study.

8.4. 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.

8.5. Investigational Product Accountability and Disposal

Accountability for lenalidomide administered during the course of the study is the responsibility of the Investigator (or designee).

Investigational clinical supplies must be received by a designated person at the study site and kept in a temperature-controlled location. Lenalidomide should be stored according to the storage conditions described on the packaging label and in a locked, safe area to prevent unauthorized access.

The Investigator (or designee) is responsible for taking an inventory of each shipment of lenalidomide received, and comparing it with the accompanying lenalidomide accountability form. The Investigator (or designee) will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and return a copy to Celgene.

The investigational site must maintain accurate records demonstrating dates and amounts of lenalidomide received, to whom it was administered (subject-by-subject accounting), and accounts of any lenalidomide accidentally or deliberately destroyed or returned. Accurate recording of all lenalidomide administration will be made in the appropriate section of the subject's CRF and source documents.

Unless otherwise notified, all lenalidomide both used and unused must be saved for IP accountability. After IP accountability has been completed by the monitor, Celgene (or designee) will review with the Investigator and relevant site personnel the process for lenalidomide return, disposal, and/or destruction including responsibilities for the site versus Celgene (or designee).

8.6. Investigational Product Compliance

All IP used by subjects will be documented by study site personnel and accurate recording of all lenalidomide used will be made in the appropriate section of the subject's CRF and source documents.

9. CONCOMITANT MEDICATIONS AND PROCEDURES

9.1. Permitted Concomitant Medications and Procedures

All supportive care is permitted, including but not limited to:

- Platelet transfusions
- Intravenous immunoglobulin
- RBC transfusions
- G-CSF per American Society of Clinical Oncology (ASCO) guidelines
- Leukapheresis
- Exchange transfusions
- Hemodialysis
- Hydration
- Allopurinol
- Sodium bicarbonate ($NaHCO_3$)
- Dexamethasone ophthalmic solution or isotears
- Pyridoxine
- Antiemetics
- Chlorhexidine solution
- Pain medications
- Antibiotics
- Anti-herpetics
- Anti-fungals
- Hydroxyurea is permitted prior to start of lenalidomide (Cycle 1 Day 1) and through Day 14 of Cycle 1 if needed to control leukocytosis. Administration will be at the discretion of the investigator.

9.2. Prohibited Concomitant Medications and Procedures

- Other chemotherapy or IP than what is specified in the protocol
- Live vaccines
- Biological therapies
- Other investigational agents

10. STATISTICAL CONSIDERATIONS

10.1. Overview

All statistical analyses will be descriptive. There will be no formal statistical comparisons due to the study being single-armed and due to a low sample size.

Secondary endpoints can only be analyzed and reported based on subjects who have had at least 6 months from study enrollment. The final analysis will be conducted once the last remaining subject in the Follow-up Phase has completed up to 5 years from the last subject's first dose.

10.2. Study Population Definitions

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 assessment post enrollment or having treatment failure before an assessment can be conducted. The RR population shall be applied to the analysis of the primary endpoint.

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 shall be applied to all treatment activity-based primary and secondary endpoints.

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.

Pharmacokinetic population

The PK population consists of all subjects receiving at least one dose of lenalidomide and having at least one measurable lenalidomide concentration.

10.3. Sample Size and Power Considerations

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 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 endpoint analysis will be used to assess the primary endpoint.

10.4. Background and Demographic Characteristics

Subjects' age, height, weight, and baseline characteristics will be summarized using descriptive statistics, while gender, race and other categorical variables will be provided using frequency tabulations. Medical history data will be summarized using frequency tabulations by system organ class and preferred term.

10.5. Subject Disposition

Subject disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent for both Treatment and Follow-up Phases. A summary of subjects enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations.

10.6. Efficacy Analysis

10.6.1. Primary endpoint

Morphologic complete response rate (CR or CRi) rate within 4 investigational product cycles

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. These response criteria will be assessed according to the revised AML IWG Criteria (Cheson, 2003).

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 (maximum likelihood estimator). 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. 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 Response Rate population. Decision making with regard to continuation to Stage 2 and at the end of Stage 2 will be based on responses within the Response Rate population.

10.6.2. Secondary endpoints

Overall Response Rate

Overall response rate defined as the proportion of subjects with CR, CRi or PR among all subjects evaluable for ORR assessment. The ORR rate at the end of Cycles 1, 2, 3, 4, 8 and 12 will be categorized, and the rate will be calculated by dividing the number of subjects completing each given cycle of interest. The corresponding Clopper Pearson 95% confidence interval will be calculated for the response rate at the end of each pre-specified cycle.

Disease Assessment Outcome

Disease assessment outcome at the end of Cycles 1, 2, 3, 4, 8 and 12 of lenalidomide administered shall be categorized according to the Cheson criteria (Cheson, 2003). The response rate for each of the best response criteria will be calculated as the total number of subjects in a given category at each time point over the number of subjects completing each corresponding cycle. The corresponding Clopper Pearson 95% confidence interval will be calculated per response category at the end of each pre-specified cycle.

Durable Response Rate

Durable response rate is defined as the proportion of subjects achieving a bone marrow confirmed CR/CRi lasting at least 3 months or until transplantation if earlier among all subjects evaluable for the durable response rate assessment. The corresponding Clopper Pearson 95% confidence interval will be calculated for the durable response rate.

Duration of Response

Duration of response is defined as the time from date of the first observed response (CR, CRi or PR) until morphologic relapse, molecular/cytogenetic relapse, or death only for subjects achieving a response. Subjects alive and leukemia-free at the time of the statistical analysis will be censored at the time of their last disease assessment. The median DoR time along with the corresponding 95% confidence interval based on Greenwood's standard error will be calculated using Kaplan-Meier methods. The proportion of subjects remaining without a DoR event at 6, 12 and 24 months will also be presented. Should the number of subjects considered for inclusion in DoR analysis fall below a third of the total sample size, the DoR shall be analyzed descriptively due to the low number of subjects available for analysis. Duration of response shall be analyzed both allowing for censoring of subjects at time of HSCT and without censoring of subjects at the time of HSCT.

Transplantation Rate

The proportion of subjects undergoing a transplant of any kind during the conduct of this study will be calculated over the total number of subjects enrolled into this study. The corresponding Clopper Pearson 95% confidence interval for the proportion of transplantations shall be calculated. Proportions shall also be calculated based on whether the transplantation is first, second, or subsequent transplants.

Subject/blast Characteristics Correlating With Response

Laboratory results obtained at diagnosis and relapse (peripheral WBC and blast count, bone marrow blast percentage, cytogenetics, molecular alterations, etc.) will be evaluated in association with response parameters by means of Pearson's rank correlation.

10.7. Safety Analysis

10.7.1. Toxicity Assessment

Toxicity will be monitored real-time through study chair notification and end of course reports. Descriptive statistics will be used to summarize the proportion of subjects experiencing any and Grade 3 or higher non-hematologic toxicities, summarize length of hospitalization time, and to estimate count recovery. This study will utilize the CTCAE version 4.03 of the NCI for toxicity grading.

10.7.2. Adverse Events

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) (updated version). The severity of AEs will be graded according to the NCI-CTCAE (version 4.03, June 2010).

Treatment-emergent adverse events are defined as any AE occurring or worsening on or after the first treatment of the study medication and within 28 days after the last dose. All TEAEs, AEs leading to study medication discontinuation, AEs leading to dose reduction/interruption, AEs related to the lenalidomide, SAEs and AE leading to death will be summarized by cycle and 28-day period after last cycle as well as by subject (worse recorded grade) per event type (organ class and preferred tern) and grade. A summary of AEs with NCI-CTCAE Grade 3 or higher, as well as the most frequent preferred terms will also be provided by grade and term.

10.7.3. Deaths

Deaths during study treatment (defined as deaths, which occur starting from the first dose and within 28 days after the last dose of study medication) and during the Follow-up Phase shall be summarized by frequency of occurrence and corresponding percentage by cause of death per period (during Treatment or Follow-up Phases) as well as overall.

10.7.4. Clinical Laboratories

Clinical laboratory adverse events will be graded according to NCI-CTCAE (version 4.03, June 2010) for applicable tests. Baseline grade and worst grade during study treatment for selected laboratory results will be summarized. Shift from baseline to the worst grade observed during the study treatment for selected laboratory results will also be provided.

10.7.5. Vital Signs

For vital signs, shift from baseline to worst during the treatment in below, within, and above the normal ranges will be displayed in cross-tabulations. Summary statistics (N, mean, standard deviation, median, minimum, and maximum) of observed and change from baseline values will be presented.

10.9. Interim Analysis

Once 4 subjects having received at least one dose of lenalidomide have completed at least 1 cycle of study treatment or discontinued treatment (whichever occurs first), the DMC will evaluate the safety data available and provide a recommendation.

An interim analysis is planned to take place 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. 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 end of Stage 1 and following safety and treatment activity data review, the DMC will 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. A DMC shall meet at least semi-annually after sufficient subject data has

been collected to review safety and treatment activity data. This close monitoring for safety of the IP will ensure a low exposure rate of the IP to subjects by ensuring the boundary of considered acceptable toxicity is not crossed.

10.9.1. Stopping Criteria for Acute Graft-Versus-Host Disease

Subjects who are post-allogeneic HSCT will be monitored closely for the development of acute graft-versus-host disease (GVHD). While Grade 1 to 2 GVHD will be tolerated, if 40% or more of subjects develop Grade 3 or higher GVHD, lenalidomide at this dose will be deemed intolerable for subjects who are post-HSCT.

10.9.2. Statistical Rationale for GVHD Stopping Criteria

The GVHD stopping rule is designed so that the trial will stop rarely when the true GVHD rate is 10% and frequently when the true GVHD rate is 40% (H0: $p = 0.10$, H1: $p = 0.40$, and alpha = 0.10, power is 90%). In this case, if 4 or more post-HSCT subjects in the first 15 develop Grade 3 or 4 GVHD, the stopping rule threshold would be crossed and further post-HSCT subjects would not be enrolled.

10.10. Pharmacokinetic Analysis

Approximately 50% of subjects should be younger than 12 years of age to provide adequate PK data for this age subset. 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 to $\leq$ 18 years).

Non-compartmental PK parameters in plasma may also be estimated using intensive lenalidomide concentration data collected from this study.

10.11. Other Topics

Not Applicable.

11. ADVERSE EVENTS

11.1. 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 below), 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 investigational product should be reported as an AE. An overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose CRF. For the definition of overdose see Section 8.2.2. Any sequelae of an accidental or intentional overdose of an investigational product should be reported as an AE on the AE CRF. If the sequelae of an overdose is an SAE, then the sequelae must be reported on an SAE report form and on the AE CRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and CRF but should not be reported as an SAE itself.

In the event of overdose or exaggerated response, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for a lenalidomide 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, physical examination findings, or other appropriate tests and procedures.

All AEs will be recorded by the Investigator from the time the subject signs ICF/IAF 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. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

11.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all AEs as to:

11.2.1. 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.

Second primary malignancies will be monitored as events of interest and must be reported as SAEs regardless of causal relationship to IP. This includes any SPM, regardless of causal relationship to IP, occurring at any time for the duration of the study, from the time of signing the ICF/IAF up to 5 years from the date of the last subject's first dose unless withdrawal of consent, lost to follow-up or death. Events of SPM are to be reported using the SAE report form and must be considered an "Important Medical Event" even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the CRF and subject's source documents. Documentation on the diagnosis of the second primary malignancy must be provided at the time of reporting as an SAE (eg, any confirmatory histology or cytology results, X-rays, CT scans, etc.).

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.

If an AE is considered serious, both the AE page/screen of the CRF and the SAE report form must be completed.

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.

11.2.2. 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 NCI CTCAE, version 4.03; (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_4003);

AEs that are not defined in the NCI 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.

In addition, for purposes of grading AST and ALT adverse events in this study, the ULN for AST is 50 U/L and the ULN for ALT is 45 U/L.

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.

11.2.3. 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.

11.2.4. Duration

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

11.2.5. 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.

11.2.6. 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, death (due to the SAE).

11.3. 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 an SAE.

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/screen of the CRF. 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).

11.4. 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.

The exposure of any pregnant female (eg, caregiver, pharmacist, study coordinator or monitor) to lenalidomide is also an immediately reportable event.

11.4.1. Female Children of Childbearing Potential and Females of Childbearing Potential

Pregnancies and suspected pregnancies (including elevated beta-human chorionic gonadotropin (β-hCG) or positive pregnancy test in a female of childbearing potential regardless of disease state) occurring while the subject is on IP, or within 28 days of the subject's last dose of IP, are considered immediately reportable events.

IP must be discontinued immediately and the subject will be 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 by email, phone, or facsimile, or other appropriate method, using the Initial Pregnancy Report Form, or approved equivalent form.

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

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 Follow-up Pregnancy Report Form, or approved equivalent form.

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

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 Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

11.4.2. Male Subjects

If a female partner of a male subject taking IP becomes pregnant, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately. The IP may need to be discontinued in the male subject, but may be resumed later at the discretion of the Investigator and Medical Monitor.

11.5. Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the CRF. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method (eg, via email), using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

Second primary malignancies will be monitored as events of interest and must be reported as SAEs regardless of causal relationship to IP. This includes any SPM, regardless of causal relationship to IP, occurring at any time for the duration of the study, from the time of signing the ICF/IAF up to 5 years from the date of the last subject's first dose unless withdrawal of consent, lost to follow-up or death. Events of SPM are to be reported using the SAE report form and must be considered an "Important Medical Event" even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the CRF and subject's source documents. Documentation on the diagnosis of the second primary malignancy must be provided at the time of reporting as an SAE (eg, any confirmatory histology or cytology results, X-rays, CT scans, etc.).

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent/assent to at least 28 days after the last dose of IP), and those 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/IAF) will be captured.

The SAE report should provide a detailed description of the SAE and include summaries of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Celgene Drug Safety as soon as these become available. Any follow-up data will be detailed in a subsequent SAE report form, or approved equivalent form, and sent to Celgene Drug Safety.

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board/Ethics Committee (IRB/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.

11.5.1. Safety Queries

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

11.6. 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 lenalidomide based on the IB.

In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

Events of disease progression for the disease under study (including death due to disease progression that are considered to be fatal) will be assessed as expected adverse events and will not be reported as expedited safety reports to regulatory authorities.

Celgene 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 15.3 for record retention information).

Celgene Drug Safety Contact Information:

For Celgene Drug Safety contact information, please refer to the Serious Adverse Event Report Form/Completion Guidelines or to the Pregnancy Report Form/Completion Guidelines.

12. DISCONTINUATIONS

12.1. Treatment Discontinuation

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

- Adverse Event
- Withdrawal by parent/guardian(s)/subject
- Death
- Lost to follow-up
- Pregnancy
- Non-compliance with IP
- Physician decision
- Protocol violation
- Other

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.

12.2. Study Discontinuation

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

- Screen failure
- Adverse Event
- Withdrawal by parent/guardian(s)/subject
- Death
- Lost to follow-up
- Other

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

All subjects who are withdrawn from the study should complete all protocol-required evaluations scheduled for treatment discontinuation at the time of withdrawal.

Since the follow-up of subjects who discontinue prematurely is of particular importance, every attempt should be made to collect all survival information and AML treatment/therapy, unless the subject has specifically withdrawn consent from further follow-up. The Investigator must make every effort to obtain minimal information regarding the subject's survival status before determining the subject is lost to follow-up.

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 70 sites.

13. EMERGENCY PROCEDURES

13.1. Emergency Contact

In emergency situations, the Investigator should contact the responsible Clinical Research 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 Research 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 Research Physician(s) or Medical Monitor (or designee) for emergency calls.

13.2. Emergency Identification of Investigational Products

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

14. REGULATORY CONSIDERATIONS

14.1. 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 International Conference on Harmonisation (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.

14.2. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. Celgene 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 Celgene 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)/informed assent form (IAF) and are screened for entry into the study. Subjects who fail 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 Celgene on public registry websites) is considered Celgene confidential information. Only information that is previously disclosed by Celgene on a public registry website may be freely disclosed by the Investigator or its institution, or as outlined in the Clinical Trial Agreement. Celgene 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 Celgene. Information proposed for posting on the Investigator's or their institution's website must be submitted to Celgene 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, Celgene 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.

14.3. Subject Information and Informed Consent

The Investigator must obtain informed consent/pediatric assent of the subject and/or the subject's legal representative(s) prior to any study-related procedures.

Documentation that informed consent/pediatric assent 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 informed consent form/informed assent form and/or the informed consent of the subject's legal representative(s) signed and dated by the study subject, the subject's legal representative(s) 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/legal representative(s).

In the case where a study center has an IRB- and Celgene-approved procedural ICF/IAF that allows collection of additional bone marrow samples for potential research purposes, the latest pre-study PB and BM aspirate/biopsy may be used for screening study assessments.

In addition, if a protocol is amended and it impacts on the content of the informed consent/informed assent, the informed consent/informed assent form must be revised. Study subjects and/or legal representative(s) of study subject's participating in the study when the amended protocol is implemented must be reconsented with the revised version of the informed consent/informed assent form. The revised informed consent/informed assent form and/or the informed consent of the subject's legal representative(s) signed and dated by the study subject, the subject's legal representative(s) 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 and/or legal representative(s).

14.4. Confidentiality

Celgene 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). Celgene requires the Investigator to permit Celgene'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 informed consent form/informed assent form, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

14.5. Protocol Amendments

Any amendment to this protocol must be approved by the Celgene Clinical Research 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's name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/EC approval but will be submitted to the IRB/EC for information purposes.

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

Before the start of the study, the study protocol, informed consent form/informed assent form, 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.

IP can only be supplied to an Investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by Celgene 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 informed consent/assent document 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 Celgene and the IRB/EC prior to use.

14.7. 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.

14.8. Termination of the Study

Celgene 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 Celgene 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.

15. DATA HANDLING AND RECORDKEEPING

15.1. Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product 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.

15.2. Data Management

Data will be collected via CRF and entered into the clinical database per Celgene 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.

15.3. 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/IAFs for all subjects;
- Subject identification code list, screening 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 Celgene 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 Celgene prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask Celgene 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.

16. QUALITY CONTROL AND QUALITY ASSURANCE

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

16.1. Study Monitoring and Source Data Verification

Celgene 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 Investigator's Meeting. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, CRFs, procedures for obtaining informed consent/assent, 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. At each monitoring visit, the facilities, investigational product storage area, CRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative for accuracy, adherence to the protocol and Good Clinical Practice.

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/assents, 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.

16.2. Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene. Representatives of this unit will conduct audits of clinical research activities in accordance with Celgene SOPs [or appropriate SOP] to evaluate compliance with Good Clinical Practice 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, EMA, 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 Celgene immediately.

17. PUBLICATIONS

As described in Section 14.2, all protocol- and amendment-related information, with the exception of the information provided by Celgene on public registry websites, is considered Celgene confidential information and is not to be used in any publications. Celgene protocol-related information proposed for use in a publication must be submitted to Celgene for review and approval, and should not be utilized in a publication without express written approval from Celgene, or as described in the Clinical Trial Agreement.

Celgene will ensure Celgene-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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19. APPENDICES

Appendix A: World Health Organization Classification of Acute Myeloid Leukemia

World Health Organization Classification
Acute Myeloid Leukemia (AML) with recurrent genetic abnormalities: • AML with t(8;21)(q22;q22); *RUNX1-RUNX1T1* • AML with inv(16)(p13;q22) or t(16;16)(p13;q22); *CBFB-MYH11* • Acute promyelocytic leukemia with t(15;17)(q22;q11-12); *PML-RARα* • AML with t(9;11)(p22;q23); *MLLT3-MLL* • AML with t(6;9)(p23;q34); *DEK-NUP214* • AML with inv(q21;q26.2) or t(q21;q26.2); *RPN1-EVI1* • AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1* • Provisional entity: AML with mutated *NPM1* • Provisional entity: AML with mutated *CEBPA*
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasm
AML not otherwise categorized: • AML with minimal differentiation • AML without maturation • AML with maturation • Acute promyelocystuc leukemia • Acute myelomonocytic leukemia • Acute monoblastic and monocytic leukemia • Acute erythroid leukemia • Acute megakaryoblastic leukemia. • Acute basophilic leukemia. • Acute panmyelosis with myelofibrosis.
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Blastic plasmacytoid dendritic cell neoplasm

Source: National Cancer Institute, 2014.

Appendix B: Lenalidomide Dosing Table – Capsule

Lenalidomide* Dosing Table – Capsule							
Calculated Dose (mg/day)**	Actual Dose Administered (mg/day)	Number of Capsule Strength					
		2.5 mg	5 mg	10 mg	15 mg	20 mg	25 mg
15	15				1		
16	15				1		
17	17.5	1			1		
18	17.5	1			1		
19	20					1	
20	20					1	
21	20					1	
22	20					1	
23	22.5	1				1	
24	25						1
25	25						1
26	25						1
27	25						1
28	27.5	1					1
29	30		1				1
30	30		1				1
31	30		1				1
32	30		1				1
33	35			1			1
34	35			1			1
35	35			1			1
36	35			1			1
37	35			1			1
38	40					2	
39	40					2	
40	40					2	
41	40					2	
42	40					2	
43	45					1	1
44	45					1	1
45	45					1	1
46	45					1	1
47	45					1	1
48	50						2
49	50						2

Lenalidomide* Dosing Table – Capsule							
Calculated Dose (mg/day)**	Actual Dose Administered (mg/day)	Number of Capsule Strength					
		2.5 mg	5 mg	10 mg	15 mg	20 mg	25 mg
50	50						2
51	50						2
52	50						2
53	52.5	1					2
54	55		1				2
55	55		1				2
56	55		1				2
57	60					3	
58	60					3	
59	60					3	
60	60					3	
61	60					3	
62	60					3	
63	65				1		2
64	65				1		2
65	65				1		2
66	65				1		2
67	65				1		2
68	70					1	2
69	70					1	2
70	70					1	2

* Using CC-5013 strengths: 2.5 mg (Size 4), 5 mg (Size 2), 10 mg (Size 0), 15 mg (Size 0), 20 mg (Size 0) and 25 mg (Size 0).

** If the calculated dose falls between two integers, the dose calculated should be rounded up or down to the nearest whole number. The actual dose to be administered can be determined after rounding the calculated dose.

Appendix C: Lenalidomide Dosing Table – Oral Suspension

Calculated Dose (mg/day)	Actual Dose Administered (mg/day)	Volume Administered (mL)
15	16	1.6
16	16	1.6
17	18	1.8
18	18	1.8
19	20	2
20	20	2
21	22	2.2
22	22	2.2
23	24	2.4
24	24	2.4
25	26	2.6
26	26	2.6
27	28	2.8
28	28	2.8
29	30	3
30	30	3
31	32	3.2
32	32	3.2
33	34	3.4
34	34	3.4
35	36	3.6
36	36	3.6
37	38	3.8
38	38	3.8
39	40	4
40	40	4
41	42	4.2
42	42	4.2
43	44	4.4
44	44	4.4
45	46	4.6
46	46	4.6
47	48	4.8
48	48	4.8
49	50	5
50	50	5

Calculated Dose (mg/day)	Actual Dose Administered (mg/day)	Volume Administered (mL)
51	52	5.2
52	52	5.2
53	54	5.4
54	54	5.4
55	56	5.6
56	56	5.6
57	58	5.8
58	58	5.8
59	60	6
60	60	6
61	62	6.2
62	62	6.2
63	64	6.4
64	64	6.4
65	66	6.6
66	66	6.6
67	68	6.8
68	68	6.8
69	70	7
70	70	7

Appendix D: Modified International Working Group AML Response Criteria

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/μL and platelets ≥100,000/μL 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/μL. • Platelets < 100,000/μL or > 100,000/μL 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/μL and platelets ≥ 100,000/μL 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.

Hematologic Response According to IWG Criteria for AML	
Category	**Definition**
Treatment Failure	**Resistant Disease**: Patient survives ≥ 7 days post-therapy and failed to achieve CR, CRi, or PR with persistent AML in blood or bone marrow. **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.

Appendix E: KARNOFSKY PERFORMANCE STATUS

Numeric Score Representing the Functional Capabilities of a Person 16 Years and Older (≥16 years) According to the Karnofsky Scale

Score	Description
100	Normal; no complaints; no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self; unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled; requires special care and assistance.
30	Severely disabled; hospitalization is indicated although death not imminent.
20	Very sick; hospitalization necessary; active support treatment necessary.
10	Moribund; fatal processes progressing rapidly.
0	Dead.

Source: Karnofsky, 1948.

Appendix F: LANSKY PERFORMANCE STATUS

Numeric Score Representing Performance Status of a Subject 0-15 Years of Age (<16 years) According to the Lansky Scale

Score	Description
100	Fully active, normal.
90	Minor restrictions in physically strenuous activity.
80	Active, but tires more quickly.
70	Both greater restriction of, and less time spent in, active play.
60	Up and around, but minimal active play; keeps busy with quieter activities.
50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
40	Mostly in bed; participates in quiet activities.
30	In bed; needs assistance even for quiet play.
20	Often sleeping; play entirely limited to very passive activities.
10	No play; does not get out of bed.
0	Unresponsive.

Source: Lansky, 1987.

Appendix G: List of Abbreviations and Definitions of Terms

ABC	Activated B Cell
ADE	Daunorubicin, Cytarabine, Etoposide
AE	Adverse Event
ALL	Acute Lymphoblastic Leukemia
ALT (SGPT)	Alanine Transaminase (Serum Glutamate Pyruvic Transaminase)
AML	Acute Myeloid Leukemia
AMP	Adenosine Monophosphate
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
AST (SGOT)	Aspartate Transaminase (Serum Glutamate Oxaloacetic Transaminase)
AUC	Area Under the Concentration-Time Curve
β-hCG	Beta-Human Chorionic Gonadotropin
BMA	Bone Marrow Aspirate
BMT	Bone Marrow Transplant
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CEBP-alpha	CCAAT/Enhancer-binding Protein alpha
CBC	Complete Blood Count
CDC	Center for Disease Control
CLcr	Creatinine Clearance
CL/F	Apparent Total Clearance
CLL	Chronic Lymphocytic Leukemia
Cmax	The Maximum Concentration
CML	Chronic Myeloid Leukemia
CN-AML	Cytogenetically Normal Acute Myeloid Leukemia
CNS	Central Nervous System
CR	Complete Remission
CRBN	Cereblon
CRF	Case Report Form
CRi	CR with Incomplete Blood Count Recovery
CRO	Clinical Research Organization
CRT	Chemoradiation Therapy
CSF	Cerebrospinal Fluid
CT	Computed Tomography

CTCAE	Common Terminology Criteria For Adverse Events
CUL4	Cullin 4
DDB1	DNA Damage-binding Protein 1
DLBCL	Diffuse Large B Cell Lymphoma
DLI	Donor Lymphocyte Infusion
DLT	Dose Limiting Toxicities
DMC	Data Monitoring Committee
DOB	Date of Birth
EC	Ethics Committee
ECG	Electrocardiogram
EFS	Event-free Survival
EGTA	Ethylene Glycol Tetraacetic Acid
EMA	European Medicines Agency
FAB	French-American-British Classification
FCBP	Female of Childbearing Potential
FCCBP	Female Children of Childbearing Potential
FDA	Food and Drug Administration
FISH	Fluorescent In Situ Hybridization
FLT3	Fms-like tyrosine kinase 3
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony Stimulating Factor
GFR	Glomerular Filtration Rate
GPR68	G protein-Coupled Receptor 68
GI	Gastrointestinal
GVHD	Graft Versus Host Disease
HIV	Human Immunodeficiency Virus
HSCT	Hematopoietic Stem Cell Transplant
IAF	Informed Assent Form
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference On Harmonisation
ICU	Intensive Care Unit
IIT	Investigator Initiated Trial
IL	Interleukin
IFN	Interferon

IP	Investigational Product
IRB	Institutional Review Board
IRF4	Interferon Factor 4
IST	Immune Suppressive Therapy
IT	Intrathecal
ITT	Intention to Treat
IV	Intravenous
IWG	International Working Group
IWRS	Interactive Web Response System
JAK	Janus Kinase
LDH	Lactate Dehydrogenase
LMWH	Low-Molecular-Weight Heparin
MA	Mitoxantrone, Cytarabine
MCL	Mantle Cell Lymphoma
M-CSF	Macrophage Colony-Stimulating Factor
MCV	Mean Corpuscular Volume
MDF	Multidimensional Flow Cytometry
MDS	Myelodysplastic Syndromes
MDSL	MDS Patient-derived Cell Line
MedDRA	Medical Dictionary for Regulatory Activities
miRNA	Microribonuleic Acid
MLL	Mixed Lineage Leukemia
MM	Multiple Myeloma
MRD	Minimal Residual Disease
mRNA	Messenger Ribonucleic Acid
MTD	Maximum Tolerated Dose
MYD88	Myeloid Differentiation Primary Response Gene (88)
$NaHCO_3$	Sodium Bicarbonate
NCI	National Cancer Institute
NF-κB	Nuclear Factor kappa-Light-Chain-Enhancer of Activated B Cells
NHL	Non-Hodgkin's Lymphoma
NK	Natural Killer (T-Cell)
NPM1	Nucleophosmin
OEP	Optional Extension Phase

ORR	Overall Response Rate
PK	Pharmacokinetics
PR	Partial Response
RBC	Red Blood Cell (Count)
Roc 1	Regulator of Cullins 1 Protein
RR	Response Rate
rrAML	Relapsed or Refractory Acute Myeloid Leukemia
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sCr	Serum Creatinine
SCT	Stem Cell Transplantation
SD	Stable Disease
shRNAs	Small Hairpin RNA or Short Hairpin RNA
siRNA	Small Interfering Ribonucleic Acid
SOP	Standard Operating Procedures
SPID	Surgical Pathology Identification Number
SPM	Second Primary Malignancy
SUSARs	Suspected Unexpected Serious Adverse Reactions
SWOG	Southwest Oncology Group
TEAE	Treatment-emergent Adverse Event
t_{max}	Time of Maximum Exposure
TEN	Toxic Epidermal Necrolysis
TFR	Tumor Flare Reaction
TLS	Tumor Lysis Syndrome
TNF	Tumor Necrosis Factor
TPN	Total Parenteral Nutrition
TTP	Thrombotic Thrombocytopenic Purpura
$t_{1/2}$	Half-life
ULN	Upper Limit of Normal
UMVUE	Uniformly Minimum Variance Unbiased Estimator
US	United States
USPI	United States Prescribing Information
VOD	Veno-occlusive Disease
WBC	White Blood Cell (Count)

WHO	World Health Organization
XRT	Palliative Radiation Therapy

Appendix H: Lenalidomide Plasma* PK Sample Handling Instructions

Preparation of Collection Tubes and Storage Vials

All labels will be provided by central lab. The labels will contain the following information:

- Protocol No.: **CC-5013-AML-002**
- Subject ID number: (To be added by site)
- Treatment: Lenalidomide
- Nominal Time: eg, 1 hour after dosing
- Sample Type: **Plasma,**

All blood, plasma collection tubes and storage vials should be labeled and chilled on wet ice **prior to** sample collection and processing.

Lenalidomide Plasma PK Sample Handling

1. **Blood Sample Collection**
   - Fill an ice bucket with a sufficient amount of ice to pre-chill all collection tubes before blood draw.
   - Collect approximately 1 mL of whole blood into a pre-chilled **K2 EDTA** tube.
   - Accurately record the time of blood collection.
   - Gently invert the tube 3 to 5 times and immerse it into ice bath immediately to prevent possible compound degradation at room temperature.
2. **Blood Sample Processing to Obtain Plasma**
   - **Within 30 minutes of collection**, the blood sample must be centrifuged at 1,500 g (about 3,000 rpm) for 10 minutes at 4°C to obtain plasma.
   - Transfer approximately 0.25 mL of plasma into each of the pre-labeled, pre-chilled, polypropylene storage tubes (ie, primary and back up). Keep storage tubes on ice before they are ready to be transferred into a freezer.
   - **Within 60 minutes of blood collection**, transfer plasma samples in storage vials into a –70ºC freezer, where they will remain stored until shipping.
   - Immediately record the time of sample entry into the freezer.

Plasma PK Sample Shipment

All PK sample label information on the storage tubes have to be checked against the requisition form and then the samples must be shipped from the sites on dry ice to the central lab.

A copy of the completed specimen manifest must accompany the shipment, and must list the following information at minimum:

- Sponsor name: Celgene Corp
- Celgene Study Number: CC-5013-AML-002
- Subject ID Numbers
- Collection date (ie, dd mmm yyyy)
- Nominal collection time (ie,1 hour, post dose)
- Sample types (eg, plasma,)

The central lab will then ship the samples to for sample analysis.

*Only 5 PK blood samples will be taken from subjects with weight ≤ 20 kg at the specified time points and seven PK blood samples will be taken from subjects with weight > 20 kg.

Appendix I: Central Pathology Review

For this study, acute myeloid leukemia will be classified according to the WHO criteria. Submit slides, all pertinent institutional reports and the CC-5013-AML-002 pathology transmittal form to the bio-pathology center as described below. These samples should be submitted within 7 days of the procedure.

REQUIRED STUDIES FOR ALL SUBJECTS AT BASELINE

1. A completed pathology report, bone marrow aspirate/biopsy report, and flow cytometry report.
2. One (1) peripheral blood smear (Wright-Giemsa stained).
3. A concurrent complete blood count including white blood cell differential (manual or automated).
4. One (1) representative bone marrow aspirate smear (Wright-Giemsa stained).
5. One (1) H&E stained slide from bone marrow clot section and/or one (1) stained slide from core biopsy.
6. Four (4) unstained slides from aspirate smears.
7. Four (4) unstained slides from clot section and/or core biopsy (preferably on charged slides).
8. Cytogenetic report, FISH studies and molecular testing (FLT3, CEPBA, NPM1, exome sequencing (if performed)).

RECOMMENDED ADDITIONAL MATERIALS:

1. Additional aspirate smears (stained and/or unstained).
2. Cytochemical stains (myeloperoxidase, non-specific esterase, PAS).
3. Immunohistochemical stains (ex.CD34, CD74, CD117, myeloperoxidase).
4. Tissue blocks.

CENTRAL PATHOLOGY REVIEW MATERIALS WILL BE RETAINED BY AND WILL NOT BE RETURNED UNLESS OTHERWISE INDICATED ABOVE.

Instructions for Labeling Slides

Bone Marrow Slides (aspirate smears, core biopsy, and clot section) - Please label bone marrow slides with the subject's 7-digit study ID number and the surgical pathology identification (SPID) number (eg, specific specimen number) from the matching bone marrow report.

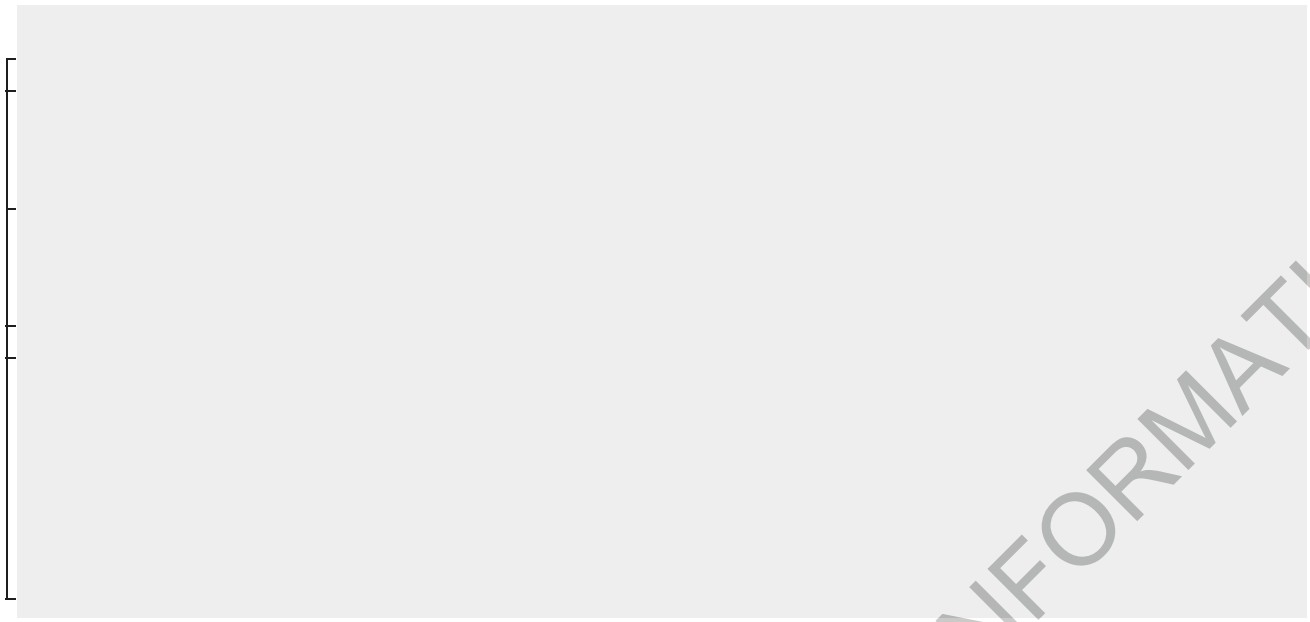
***Peripheral Blood Slides (Smears*)** - If there is a procedure or report number on the institutional laboratory report, please label the peripheral blood slides with the subject's 7-digit study ID Number and the report (or procedure) number from the institutional report. If there is not a number on the report, then please label the slide with the date the blood was drawn and the subject's 7-digit study ID Number.

Ship materials by regular mail or using your institution's courier account to the Biopathology Center:

ATTN: Celgene CC-5013-AML-002 Study

Phone:

**Be sure to include the room number. Packages received without the room number may be returned to the sender.



Appendix L: Optional Extension Phase

Subject Eligibility

At the Investigator's discretion and with approval of the Sponsor, subjects meeting all of the following eligibility criteria are eligible to enter the Optional Extension Phase:

- Subjects have received oral lenalidomide for 12 cycles and are continuing to have response or demonstrating clinical benefit from therapy as assessed by the Investigator without unacceptable toxicities.
- Subjects who have signed the informed consent for the extension phase.
- Subjects who do not meet any of the criteria for treatment discontinuation (see Section 12).
- All subjects must be counseled about pregnancy precautions and risks of fetal exposure prior to the start of lenalidomide and during IP treatment and 28 days after last dose of IP. They must also be counseled against sharing IP and donating blood during and within 28 days of discontinuing IP.
- For FCCBP/FCBP subjects, the pregnancy tests are negative when performed within 10-14 days and within 24 hours prior to the start of lenalidomide.

Subjects will start the extension study at the time of the next regularly scheduled dosing cycle.

Dosage for First Treatment Cycle

The dose and schedule for the first treatment cycle should be administered at the identical dose as the final treatment phase cycle. If a dose reduction was required in the last cycle of the treatment phase, the first treatment phase cycle should be administered at the identical (reduced) dose/or schedule. Capsules of same strengths used in the treatment phase will be utilized in the OEP. The oral suspension will be available for use in subjects who are unable to swallow the capsules or at the discretion of the investigator in the OEP.

Study Duration of the OEP

Subjects may continue to receive oral lenalidomide in the OEP until they meet the criteria for study discontinuation (Section 12).

Subsequent Treatment Cycles

Cycles should be repeated every 28 days. Subjects should be monitored for AEs, SPMs, pregnancy testing for FCCBP and FCBP, concomitant medications/procedures collection, IP dispensing (for each 28-day cycle), and IP accountability.

Oral lenalidomide Dispensing and Administration in the OEP

Subjects will be dispensed only one cycle of oral lenalidomide at a time (typically within an approximate 28-day period). All subjects should not extensively handle the lenalidomide capsules or oral suspension. The lenalidomide capsules should not be broken, chewed, or opened and should be maintained in the packaging until ingestion. Subjects will be instructed to inspect each capsule and only take capsules that are totally intact. Subjects should be instructed to return any capsule that is not totally intact to the study clinic.

Detailed instructions on preparation, administration, and handling of the lenalidomide oral suspension will be provided in a separate manual.

The dose and schedule for the first dose of treatment cycle in the OEP should be administered at the same dose and schedule as the final treatment cycle (Cycle 12). If a dose modification was required in the last cycle of the treatment phase, the first extension cycle should be administered at the identical (modified) dose and/or schedule. For dose modifications refer to Section 8.2.1.

Management of Toxicity and Dose Modifications

The subject's dose of lenalidomide should be calculated on the first day of each dosing cycle based on weight. If a subject's body weight changes by more than 10% compared with baseline body weight, or compared with a previous body weight value that required a dose adjustment, then the dose of IP should be recalculated. The dose of lenalidomide **during** a treatment cycle in the OEP should not be altered.

Hematological and non-hematological toxicity will be graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. In all cases, the reason for dose modification must be recorded in the subject's medical record. If the subject discontinues the protocol-prescribed therapy because of an AE, this event must be reported in accordance with the procedures outlined in Section 11.

Prior and Concomitant Medications and Therapy in the OEP

Refer to Section 9 for permitted and prohibited concomitant therapies.

Adverse Event Reporting

Adverse events should be reported and managed as per Section 11.

Second primary malignancies (SPMs) will be monitored as events of interest and should be included as part of the assessment of AEs throughout the course of the study. Investigators are to report any SPM as SAEs regardless of causal relationship to lenalidomide, occurring at any time for the duration of the study, from the time of signing the ICF/IAF until all subjects have been followed for up to 5 years from the last subject's first dose, unless consent is withdrawn, the subject is lost to follow-up or dies. Events of SPM are to be reported using the SAE report form and must be considered an "Important Medical Event" even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the CRF and subject's source documents. Documentation on the diagnosis of the SPM must be provided at the time of reporting as a SAE (eg, any confirmatory histology or cytology results, X-rays, computed tomography [CT] scans, etc.).

Concomitant Medications

All concomitant medications that are necessary for the subject's welfare and are unlikely to interfere with lenalidomide may be given at the Investigator's discretion during the extension study. However, treatment with any other investigational medication is not permitted.

Investigational Product Accountability and Disposal

The investigational site must maintain accurate records demonstrating dates and amounts of lenalidomide received, to whom it was administered (subject-by-subject accounting), and accounts of any lenalidomide accidentally or deliberately destroyed or returned. Accurate

recording of all lenalidomide administration will be made in the appropriate section of the subject's CRF and source documents.

Unless otherwise notified, all lenalidomide both used and unused must be saved for IP accountability. After IP accountability has been completed by the monitor, Celgene (or designee) will review with the Investigator and relevant site personnel the process for lenalidomide return, disposal, and/or destruction including responsibilities for the site versus Celgene (or designee).

Investigation Product Compliance

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

Females of child bearing potential (FCBP) should not handle or administer lenalidomide unless they are wearing gloves. All subjects should not extensively handle lenalidomide capsules or oral suspension. All subjects should not break, chew, or open lenalidomide capsules and should maintain storage of capsules in the packaging until ingestion. Refer to the subject diary and the manual on preparation, administration, and handling of the lenalidomide oral suspension for specific details.

In investigational studies, lenalidomide will be dispensed through a qualified healthcare professional (including but not limited to, nurses, pharmacists and physicians). These healthcare professionals will be trained by Celgene in requirements specific to counseling of subjects. Once trained these healthcare staff will counsel subjects prior to lenalidomide being dispensed to ensure that the subject has complied with all requirements (including use of birth control and pregnancy testing for FCBP) and that the subject understands the risks associated with lenalidomide. This step will be documented with a completed Education and Counseling Guidance Document and no lenalidomide will be dispensed until this step occurs. Counseling includes verification with the subject that required pregnancy testing was performed and results were negative.

A Lenalidomide Information Sheet will be supplied each time lenalidomide is dispensed.

Recommended Monitoring of Subjects

1. Complete blood count with WBC differential and platelet count as needed.
2. Additional tests or more frequent monitoring are at the Investigator's discretion based on the subject's clinical status.

Investigator's Responsibility

3. Complete Extension Phase Case Report Form pages.
4. Report serious adverse events (including second primary malignancies) and other immediately reportable events, as required by the protocol (see Section 11). A completed SAE form must be faxed to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event, as detailed in the Serious Adverse Event Report Form Completion Guidelines.

5. Document all adverse events (serious and non-serious) on the adverse event log page of the Extension Phase Case Report Form, as detailed by the protocol (see Section 11).
6. Report to the Sponsor drug accountability.
7. Report to the Sponsor and complete the case report form page for extension phase termination when the subject completes, discontinues, or terminates treatment.
8. The subject must stop the treatment if any of the following occur:
    a. Additional investigational treatment is started;
    b. Subject is no longer receiving clinical benefit, as per Investigator discretion;
    c. Subject withdraws consent;
    d. A CTCAE toxicity Grade 3 or 4 that represents a worsening from baseline (prior to the first dose) persists for more than 21 days, despite the temporary interruption of the regimen;
    e. A positive pregnancy test in a FCCBP/FCBP, at any time; or
    f. At the specific request of the Sponsor or its authorized representative.
9. The Investigator must be available for periodic monitoring visits and allow the Sponsor access to all medical records.
10. The Investigator will maintain source documents on the subject for all case report form data points, which include the following:
    a. Informed consent/assent;
    b. Adverse events;
    c. Dosing information (date of administration, dose);
    d. Termination date and reason.

Appendix M: Tumor Lysis Syndrome

Subjects at greatest risk are those with bulky disease or high tumor burdens with malignancies exquisitely sensitive to chemotherapy; WBC > 100,000/mL, lymphadenopathy, hepatosplenomegaly, elevated LDH, and large primary masses of the abdomen, thorax, or mediastinum. Diseases most commonly associated with TLS include Acute Lymphoblastic Leukemia (ALL), T-cell Leukemia/Lymphoma and Non-Hodgkin's Lymphoma (eg, Burkitt's lymphoma), although it can occur in tumors such as neuroblastoma where the bone marrow is completely replaced by tumor. The risk for serious acute TLS is usually restricted to the first 72 hours after initiation of therapy; however, it may spontaneously occur prior to treatment.

TLS is characterized by severe hyperuricemia, hyperphosphatemia, hyperkalemia, hypocalcemia, and acute renal failure. Suggested initial studies to be obtained prior to initiating therapy include CBC, prothrombin and activated partial thromboplastin times, fibrinogen, D-dimer, and serum electrolytes (including creatinine, BUN, uric acid, phosphorous, and calcium). Imaging pretreatment may include an abdominal ultrasound to assess renal parenchymal infiltration, as occasionally there may also be an obstructive element due to tumor pressure, and a chest X-ray including lateral to assess for mediastinal mass and tumor burden. Continued monitoring of these studies should be carried out at suitable intervals until abnormalities have resolved or the risk has abated.

Prevention and Monitoring

1. Maintain strict attention to subject's fluid balance (input and output).
2. Hydration with 2400 - 3000 mL/m^2/day of IV fluid (D5 ¼ or D5 ½) NS (no potassium) + $NaHCO_3$ 25 - 100 mEq/L. Adjust bicarbonate to maintain urine pH 6.5 - 7.5 and not in excess of 8.5 for subjects taking allopurinol. No potassium should be administered until tumor lysis is controlled. Alkalinization is not recommended when treating with uricase or rasburicase.
3. Begin allopurinol prior to chemotherapy. Allopurinol should be infused in a separate IV line from the chemotherapy. Continue until peripheral blasts and extramedullary disease are reduced.

Dose: Daily doses > 300mg should be administered in divided doses.

Children < 10 years:

- IV: 200 mg/m^2/day in 1 - 3 divided doses; maximum dose: 600 mg/day.
- PO: 10 mg/kg/day in 2 - 3 divided doses or 200 - 300 mg/m^2/day in 2 - 3 divided doses.

Maximum dose: 800 mg/day.

Children > 10 years and adults:

- IV: 200 - 400 mg/m^2/day in 1 - 3 divided doses; maximum dose: 600 mg/day.
- PO: 600 - 800 mg/day in 2 - 3 divided doses.

4. In some situations it may be appropriate to use rasburicase (recombinant urate oxidase) as initial therapy, such as in subjects who are at a significant risk of TLS due to disease or

subject-related risk factors or those who are demonstrating signs of evolving TLS. Subjects who present with renal insufficiency (serum creatinine [sCr] > 0.7 mg/dL in children or > 1.3 mg/dL in adults), either preexisting or due to new disease, and subjects with hyperuricemia at presentation are also good candidates for upfront rasburicase. Dosing for rasburicase is 0.15 - 0.2 mg/kg/dose IV over 30 minutes daily until uric acid levels have normalized and subject is clinically stable; typically 1 to 3 days. Sodium bicarbonate is not required when using rasburicase. Rasburicase is contraindicated in subjects with glucose-6-phosphate dehydrogenase (G-6PD) deficiency.

5. Check subject's urine for specific gravity and hematuria after every void.
6. Assess subject's weight twice daily.
7. Assess the subject's vital signs frequently, at a minimum every 4 hours and observe subject for irregular pulse and decrease in blood pressure.
8. Monitor the subject's laboratory values (ie, electrolytes, calcium, uric acid, creatinine, and phosphate) at least every 8 hours.
9. Hyperkalemia (> 6.0 mEq/L) leads to ventricular arrhythmias and possibly death.

   a. Assess for symptoms of cardiac arrhythmias by using a cardiac monitor if clinically indicated.

   b. Calcium administration is the fastest means of reversing the cardiac effects of hyperkalemia. Onset of action is within minutes but the duration is only one-half hour. Consider slow infusions and in a separate line from the sodium bicarbonate.

   c. Sodium bicarbonate as well as insulin and glucose administration will move excess potassium into the cell; administer sodium bicarbonate at 1 - 2 mEq/kg IV or administer continuous glucose infusion at 0.5 g/kg/hour with insulin 0.1 unit/kg/hour.
10. Maintain urine output >100 mL/m^2/hour administering mannitol 0.5 g/kg or furosemide 1 - 2 mg/kg by IV as needed.
11. If urine output declines, an ultrasound study of the kidney may be useful to rule out tumor infiltration or obstructive uropathy.
12. Perform a minimum of 1 daily physical exam for signs of dyspnea, rales, wheezing, cardiac arrhythmias, edema, ascites, neuromuscular changes, and gastrointestinal complaints.
13. Minimize exogenous potassium and phosphorous intake.
14. Avoid IV contrast and nephrotoxic medications when possible.
15. Medical management of hypocalcemia, hyperphosphatemia, hypercalcemia, and/or renal failure should be undertaken aggressively and in consultation with nephrology and the intensive care unit (ICU).
16. Monitor calcium-phosphorus product; if > 60 discontinue alkalinization.

Additional Procedures:

1. More aggressive hydration, leukapheresis, or exchange transfusion may be considered for elevated WBC (> 100,000 to 200,000) and multiple metabolic abnormalities.

2. Dopamine 3 mcg/kg/minute may aid in increasing renal blood flow.
3. Hemofiltration or dialysis may be warranted.

Dialysis indications when above fail:

a. QRS interval widening with serum potassium > 6 mEq despite kayexalate and rising creatinine with urine output < 60 mL/m^2/hour.
b. Serum uric acid > 10 mg/dL with rising creatinine and urine output < 60 mL/m^2/hour.
c. Serum creatinine > 10 mg/dL.
d. Serum phosphorus > 10 mg/dL or rapidly rising despite aluminum hydroxide with rising creatinine and urine output < 60 mL/m^2/hour.
e. Volume overload.
f. Symptomatic hypocalcemia with hyperphosphatemia.

Celgene Signing Page

This is a representation of an electronic record that was signed electronically in Livelink. This page is the manifestation of the electronic signature(s) used in compliance with the organizations electronic signature policies and procedures.

UserName:
Title:
Date: Wednesday, 14 December 2016, 07:31 AM Eastern Daylight Time
Meaning: Approved, no changes necessary.
==========

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- Removed progressive disease as part of the response criteria to avoid confusion with the overlapping definition of treatment failure. Progressive disease adds no utility in addition to treatment failure in the criteria. Language was updated throughout the document to align with the modified response criteria, including the use of the term 'relapse' and the deletion of 'resistant disease' (Protocol Summary, Table 2, Sections 4.1, 4.4, 6.20.1, 6.20.3, 6.20.4, 8.2, 8.2.1, 10.2, 10.6.2, 10.8, 12.1, Appendix D and G).
- Clarified that if clinically inappropriate per the treatment site, a subject may have the bone marrow evaluation omitted at treatment discontinuation if peripheral blast results are collected (Table 2 and 6.22).
- Clarified that subjects demonstrating clinical benefit as per the Investigator at the end of Cycle 4 and beyond may continue to receive lenalidomide on study for up to 12 cycles in the absence of protocol-defined toxicity, or transitioning to allogeneic HSCT (Protocol Summary, Sections 4.1, 4.4, 6.20.1). Clarified that subjects who do not demonstrate clinical benefit as per the Investigator at the end of Cycle 4 and beyond will be discontinued from lenalidomide treatment (Section 8.2.1).
- Updated the ALT/AST inclusion criteria by providing a specific upper limit of normal (ULN), as well as updated ULN for ALT/AST when considering dose reduction/interruption and AE grading (Sections 7.2, 8.2.1, 11.2.2).
-

The amendment also includes typographical and formatting corrections, and several other minor clarifications and corrections, including:

- The brand name of REVLIMID was capitalized throughout the document to maintain consistency (Protocol Summary, Sections 6.25 and 18).
- Updated the word 'relapse' to 'relapsed' throughout the document (Section 1.4.2 and Table 2)
- Added '(with second or greater relapse or refractory to at least 2 prior induction attempts)' as part of the primary objective to align with Section 2 (Section 1.4.2).
- Amended wording from 'summaries' to 'summarized' under Molecular and Cellular Measurements (Section 10.8).

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- The Medical Monitor/Emergency Contact Information section was updated.
- Duration of response was added as a secondary endpoint (Protocol Summary, Sections 2.2, 3.2, 10.6.2).
- Updated the number of study sites from 75 to 70 to better reflect the number of sites involved with the study (Protocol Summary, Sections 4.1, 7.1, 12.2).
- Provided clarification language to state the DMC will evaluate available safety data and provide a recommendation once 4 subjects having received at least one dose of lenalidomide have completed at least 1 cycle of study treatment or discontinued treatment (whichever occurs first) (Protocol Summary, Sections 4.1, 4.4, 10.9).
- Amended the word 'banked' to 'stored' in regard to the central biorepository samples in order to clarify how samples will be handled (Protocol Summary, Sections 4.1, 5, 6.27).
- Language was added to introduce the lenalidomide oral suspension (in addition to capsule formulation). The development of the oral suspension and implementation in the study is a key binding element of the pediatric Written Request for lenalidomide. The oral suspension is available for use in subjects who are unable to swallow the capsule formulation or at the discretion of the investigator (Protocol Summary, Sections 1.3, 8.1, 8.2, 19).
- Amended language to state the pregnancy test 10 to 14 days prior to initiation of lenalidomide may be omitted, at the discretion of the investigator, for any FCCBP/FCBP who has high acuity disease requiring immediate treatment with lenalidomide. This change was made to recognize that potential subjects identified for enrollment into the study may have high acuity AML disease and may necessitate immediate treatment with lenalidomide. The pregnancy test within 24 hours prior to the first dose of lenalidomide is still required to be performed (Sections 5, 6.8, 7.2).
- Added language to allow use of pre-study PB and BM aspirate/biopsy results for screening study assessments in the case where a study center has an IRB- and Celgene-approved procedural ICF/IAF that allows collection of additional bone marrow samples for potential research purposes. This update was made to recognize that performing additional PB and BM assessments at screening may not be feasible for certain subjects (Sections 5, 6.5, 6.20.1, 14.3).
- Added absolute neutrophil count and platelet count as hematology laboratory assessments that will be recorded in the CRF. These two assessments are part of the response assessment and must be recorded in the CRF (Section 6.14.1).
- Language was added to specify handling requirements for the lenalidomide capsules and to reference a new manual on preparation, administration, and handling of the lenalidomide oral suspension (Sections 6.16, 6.17, 8.1, 8.2, 19).

- Language was added to reference the new Appendix C, which contains the dosing guidelines for the lenalidomide oral suspension (Sections 6.17, 8.2).
- IP accountability language was updated to reflect requirements to document the number of lenalidomide vials dispensed, the date dispensed, the date returned, and the number of vials returned (Section 6.18).
- Removed the inclusion criterion stating that a subject must be able to swallow intact oral capsules. This inclusion criterion was updated since the lenalidomide oral suspension will be available for subjects unable to swallow an intact capsule (Section 7.2).
- Provided clarification language for the graft-versus-host-disease inclusion criteria (Section 7.2).
- Amended protocol to allow for use of hydroxyurea prior to the first dose of lenalidomide and through Day 14 of Cycle 1. Hydroxyurea is now permitted per protocol to control leukocytosis (Sections 7.3, 9.1).
- Added language regarding the home healthcare company that can assist with the preparation and administration of the lenalidomide oral suspension (Section 8.1).
- Corrected the administrative error involving the age range for cytarabine dosing from '3-2.99' to '2-2.99' (Section 8.2 Table 5).
- Amended the "Dose Reductions/Interruptions" section in the protocol in order to provide more concise and clear dosing guidelines (Section 8.2.1)
- Updated Appendix B lenalidomide dosing table to specify that the table specifically refers to the capsule formulation (Section 19).
- Added a new Appendix C lenalidomide dosing table specifically for the oral suspension (Section 19). References to subsequent appendices were updated throughout the document.
- Removed -specific references, including registration number, from Appendix I Central Pathology Review in order to clarify which steps are involved for the central pathology review (Section 19).
- Updated the shipping address for the biopathology center in Appendix I based on new information provided by (Section 19).