A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY OF THE EFFICACY AND SAFETY OF LENALIDOMIDE (REVLIMID®) AS MAINTENANCE THERAPY FOR PATIENTS WITH B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA FOLLOWING SECOND-LINE THERAPY

(THE CONTINUUM TRIAL)

STUDY DRUG:	Lenalidomide
PROTOCOL NUMBER:	CC-5013-CLL-002
EUDRACT NUMBER:	2007-001626-27
DATE FINAL:	15 January 2008
AMENDMENT #11:	16 March 2018

[redacted]

CONFIDENTIAL

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COORDINATING PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Original Protocol: 15 January 2008

Amendment #1: 12 August 2008

Amendment #2: 23 September 2008

Amendment #3: 17 October 2008

Amendment #4: 6 May 2009

Amendment #5: 28 June 2010

Amendment #6: 4 May 2011

Amendment #7: 7 October 2011

Amendment #8: 4 October 2012

Amendment #9: 24 April 2015

Amendment #10: 13 May 2016

Amendment #11: 16 March 2018

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Original Protocol: 15 January 2008

Amendment #1: 12 August 2008

Amendment #2: 23 September 2008

Amendment #3: 17 October 2008

Amendment #4: 6 May 2009

Amendment #5: 28 June 2010

Amendment #6: 4 May 2011

Amendment #7: 7 October 2011

Amendment #8: 4 October 2012

Amendment #9: 24 April 2015

Amendment #10: 13 May 2016

Amendment #11: 16 March 2018

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2. SYNOPSIS

Name of Sponsor/Company: Celgene Corporation	
Name of Investigational Product: lenalidomide	
Protocol Number: CC-5013-CLL-002	
Protocol Title: A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY OF THE EFFICACY AND SAFETY OF LENALIDOMIDE (REVLIMID®) AS MAINTENANCE THERAPY FOR PATIENTS WITH B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA FOLLOWING SECOND-LINE THERAPY	
Indication: Maintenance therapy in subjects with relapsed or refractory B-cell chronic lymphocytic leukemia (CLL) who have achieved at least partial response (PR) to second-line therapy.	
Study Duration: Subjects randomized to the lenalidomide treatment arm and on treatment at the time of Amendment #10 may, at the discretion of the investigator, continue on lenalidomide study treatment until disease progression (PD) develops. Subjects randomized to the placebo treatment arm and on treatment at the time of Amendment #10 will enter the survival follow-up period. Subjects who discontinue study treatment prematurely for reasons other than PD and subjects who develop PD (including disease transformation) will enter the survival follow-up period. Subjects will be followed until all subjects in the study have been followed for at least 5 years from the last randomization, October 2020, (or have died/become lost to follow-up before the 5 years). <u>Amendment #11:</u> Subjects currently on lenalidomide treatment will discontinue lenalidomide treatment immediately and complete the Treatment Discontinuation assessment. The subjects will then transition to the survival follow-up period.	**Phase of development:** Phase 3
Objectives: **Primary:** • To compare the efficacy of lenalidomide *versus* placebo maintenance therapy. **Secondary:** • To evaluate the safety of lenalidomide *versus* placebo maintenance therapy.	
Study Endpoints: **Primary** • Overall Survival (OS)	

Secondary

- Safety [type, frequency, and severity of adverse events (AEs) and relationship of AEs to lenalidomide]
- Progression-free survival 2 (PFS2)

[redacted]

Study Design:

CC-5013-CLL-002 is a phase 3, multicenter, randomized, placebo-controlled, parallel-group study that will compare the efficacy and safety of oral lenalidomide maintenance therapy to that of placebo in patients with B-cell CLL who achieved at least partial response (PR) with second-line therapy. The primary efficacy objective of this study is to demonstrate superiority of lenalidomide over placebo in prolonging overall survival (OS) due to continued therapy, for all subjects, including subjects with or without poor prognostic factors, subjects of various ages and subjects with PR, nodular partial response (nPR), complete response with incomplete bone marrow recovery (CRi), complete response (CR) and minimal residual disease (MRD)-negative CR. All subjects randomized to the lenalidomide treatment arm, including those subjects who do not improve their response (PR, nPR, CRi or CR) and subjects who do not have the opportunity to improve their response further (MRD-negative CR) will be treated up to disease progression, with the objective to demonstrate prolongation of OS.

Eligible subjects must have been treated with a purine analog-, a bendamustine-, an anti-CD20-antibody-, or a chlorambucil-based regimen in first and/or second line and must have achieved at least PR to second-line induction therapy of sufficient duration. Alemtuzumab- containing regimens will also be allowed for those subjects with 17p deletion. Subjects who achieve stable disease (SD) only or who develop progressive disease (PD) at any time during induction therapy will not be eligible for participation in this study.

Approximately, three hundred twenty (320) subjects with PR, nPR, CRi, CR or MRD-negative CR will be enrolled and randomized (1:1) into two arms: placebo daily or lenalidomide 2.5 mg daily on days 1-28 of the first 28-day cycle. If the 2.5 mg dose level is well tolerated, escalation to 5 mg daily on days 1-28 of each 28-day cycle is permitted starting with the second cycle; for those subjects who tolerate well the 5 mg dose, escalation to 10 mg daily on days 1-28 of each 28-day cycle after 5 continuous cycles at 5 mg will be permitted.

Each treatment arm will be stratified according to 1) the response to second-line induction therapy (PR, nPR, CRi or CR versus MRD-negative CR); 2) age ($\leq$ 70 versus > 70 years); and 3) presence of at least one of the following poor prognostic factors: 11q deletion, 17p deletion, unmutated IgVH or β2M > 4.0 mg/L (Yes versus No versus Unknown).

The subjects randomized to the lenalidomide treatment arm will continue to receive lenalidomide study drug up to PD. Subjects who discontinue therapy, will enter the survival follow-up phase of the study. Subjects will be assessed for subsequent CLL therapies, second primary malignancies, recovery from serious adverse events (SAEs), and any new SAEs or AEs related to study procedures or prior maintenance therapy.

Subjects randomized to the placebo arm and currently on treatment at the time of Amendment #10 and patients who previously discontinued from the study drug and will be followed every 24 weeks for survival, subsequent CLL therapies, response to next therapy and progression

following next therapy, and second primary malignancies. Subjects will be followed until all subjects in the study have been followed for at least 5 years from the last randomization, October 2020 (or have died/become lost to follow-up before 5 years).

Amendment #11:

Subjects currently on lenalidomide treatment will discontinue lenalidomide treatment immediately and complete the Treatment Discontinuation assessment. The subjects will then transition to the survival follow-up period.

Screening

Subjects will sign informed consent prior to undergoing any study-related procedures. Screening assessments for protocol eligibility will be performed within 28 days prior to randomization as outlined in Table 2: Schedule of Assessments. Subjects who develop PD during screening will not be eligible to enroll into this study.

All subjects will undergo both bone marrow aspirate and bone marrow biopsy procedures during screening. MRD status will be assessed by peripheral blood and bone marrow flow cytometry at entry into the study for those subjects who achieved a complete response (CR) to second-line induction therapy. Peripheral blood flow cytometry will be performed for all subjects at entry to confirm disease diagnosis by immunophenotyping and to perform immune cell (NK and T cell) analyses. If subjects enter the study with MRD negativity, the disease diagnosis will be confirmed based on prior flow cytometry (documentation needed). MRD status, immunophenotyping, and immune cell analyses will be performed at a central laboratory.

A peripheral blood sample for direct antiglobulin test (DAT) will be collected during screening and analyzed at a central laboratory.

Before randomization, subjects will be tested for cytogenetics by FISH, IgV_H mutational status, and β2M. The β2M test will be performed during screening using a peripheral blood sample and analyzed at a central laboratory.

FISH and IgV_H testing will be performed prior to second line, during second line, in the interval between second-line therapy, and screening or during the screening period using a peripheral blood sample. Because test results cannot be obtained during screening or between second line and screening in some subjects who achieve a good response due to the limited number of remaining CLL cells, we recommend conducting the FISH and IgV_H tests preferably prior to second line or during second line.

Samples for FISH and IgV_H will be analyzed at a central laboratory.

If tests do not yield results, subjects can be randomized and stratified based on historical data.

Those subjects for whom results were not obtainable pre-randomization and for whom no historical data were available will be enrolled and grouped separately.

During screening, CT scans of the chest, abdomen and pelvis will also be performed for all subjects; in particular, they will be used to document the status (PR or CR) of subjects entering the study.

If, during the screening period, the subject has a correctable event that prevents randomization and the event cannot be corrected within the 28 day screening period, the subject may be re-screened; however, the CT scans and bone marrow aspirate and biopsy will not need to be repeated if those tests were implemented within 56 days prior to randomization and the subject's clinical status remains the same.

Randomization

Randomization must occur no less than 8 weeks (56 days) and no greater than 20 weeks (140 days) from the last day of the last cycle of second-line induction therapy received by the subject in order for the subject to be eligible for enrollment into this study. Subjects meeting all eligibility criteria will be randomized (1:1) in a double-blind manner to receive maintenance therapy with either lenalidomide or placebo up to disease progression. The randomization procedure will be accomplished by a validated interactive voice response system (IVRS). Subjects will be stratified at randomization by: 1) their response to second-line induction therapy (PR, nPR, CRi or CR versus MRD-negative CR); 2) age (≤ 70 versus > 70 years); and 3) presence of at least one of the following poor prognostic factors: 11q deletion, 17p deletion, unmutated IgVH or β2M > 4.0 mg/L (Yes versus No versus Unknown).

Maintenance Therapy

Study treatment for each subject begins on the same day the subject undergoes randomization. Study visits and serial measurements of safety and efficacy during maintenance therapy will be performed as outlined in Table 2. Lenalidomide is administered orally. Subjects will receive lenalidomide 2.5 mg once daily on Days 1 through 28 of the first 28-day cycle. If the 2.5 mg dose is well tolerated (subject does not experience any Grade 3 or 4 study drug-related toxicities or any other toxicity [Grade 1 or 2] found to be unacceptable by the investigator or the subject), subjects should be escalated starting at the second cycle to 5 mg once daily on Days 1 through 28 of each 28-day cycle up to disease. If a subject develops a Grade 1 or 2 adverse event, the drug may be interrupted until resolution, however the subject must complete one full cycle at the 2.5 mg dose level prior to escalation to the 5 mg dose level.

Subjects who complete 5 continuous cycles at the 5 mg dose level without experiencing any Grade 3 or 4 study drug-related toxicities and without experiencing any other toxicity (Grade 1 or 2) found to be unacceptable by the investigator may be escalated to 10 mg once daily on Days 1 through 28 of each 28-day cycle up to disease progression.

Dose interruptions/reductions are permitted for Grade 1 or 2 adverse events at the investigator's discretion. A guideline for the reduction of the dose of lenalidomide for dose-limiting toxicity (DLT) is provided (see Section 10.2.1). Dose re-escalation is permitted if the subject is able to complete 2 full cycles at the reduced dose level without experiencing a DLT or other toxicity deemed to be unacceptable by the investigator or subject. In the event the dose reduction is implemented due to Grade 4 neutropenia, subjects may be re-escalated after one full cycle at the lower dose level if the neutropenia resolves to a Grade 2 or better by the end of the cycle and no other DLT is observed. If that dose level is again not tolerated, the subject should be de-escalated to the dose below and remain at that tolerated dose level for the rest of the study.

Subjects randomized to the lenalidomide treatment arm will continue to receive study lenalidomide maintenance therapy until PD develops. Progressive disease is characterized by at least one of the following:

- Lymphadenopathy. Progression of lymphadenopathy discovered by physical examination. Disease progression occurs if one of the following events is observed:
  - Appearance of any new lesion such as enlarged lymph nodes (> 1.5 cm), splenomegaly, hepatomegaly or other organ infiltrates.
  - An increase by 50% or more in greatest determined diameter of any previous site.

- An increase in the previously noted enlargement of the liver or spleen by 50% or more or the de novo appearance of hepatomegaly or splenomegaly.
- An increase in the number of blood lymphocytes by 50% or more with at least 5,000 B lymphocytes per µL.
- Transformation to a more aggressive histology (eg, Richter's syndrome). Whenever possible, this diagnosis should be established by lymph node biopsy.
- Occurrence of cytopenia (neutropenia, anemia or thrombocytopenia) attributable to CLL
- During therapy: cytopenias may occur as a side effect of many therapies and should be assessed according to Table 4. During therapy, cytopenias cannot be used to define disease progression.
- Post treatment: The progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of hemoglobin levels by more than 2 g/dL or to less than 10 g/dL, or by a decrease of platelet counts by more than 50% or to less than 100,000/µL, which occurs at least 3 months after treatment, defines disease progression, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells.

Tumor response, including PD, will be assessed according to the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) guidelines for the diagnosis and treatment of chronic lymphocytic leukemia ([redacted] The severity of AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0 with modifications as noted in Section 10.2.1 of the protocol.

Local hematology and chemistry tests will be performed for patient management/treatment decisions.

Bone marrow aspirate and biopsy specimens obtained from each subject will be reviewed centrally prior to randomization. All repeat bone marrow aspirate and biopsy assessment will be completed at the discretion of the investigators and assessed locally. The bone marrow aspirate and biopsy assessment is removed as part of protocol amendment #10.

The CT scans of the chest, abdomen and pelvis will be performed for all subjects at baseline. All repeat CT scan assessment will be completed at the discretion of the investigator and assessed locally. The CT scan assessment is removed as part of protocol amendment #10.

Amendment #11:

Subjects currently on lenalidomide treatment will discontinue lenalidomide treatment immediately and complete the Treatment Discontinuation assessment. The subjects will then transition to the survival follow-up period.

Prophylaxis for Tumor Lysis Syndrome (TLS), thromboembolism and infection and treatment of tumor flare reaction (TFR)

TLS prophylaxis, comprising of oral hydration and allopurinol 300 mg/day will be initiated 3 days prior to starting maintenance therapy and for a minimum of the first treatment cycle at each dose level for those subjects entering the study with a PR to their second-line induction therapy. Subjects with a known allergy to allopurinol and a PR will be excluded from the study. Please refer to Section 10.2.1 for further guidance on allopurinol modification in the event of an adverse event. If a subject is taking allopurinol for a condition other than for TLS prophylaxis, the subject should be continued on the allopurinol prescribed by their

physician and the dose titrated to 300 mg/day. If, at any time, the allopurinol being taken for reasons other than TLS prophylaxis is discontinued and prophylaxis is still required per protocol, the subject should be administered commercial allopurinol. To maintain fluid intake, subjects must be instructed to drink 8 to 10 eight ounce (240 mL) glasses of water each day for the first 14 days of Cycle 1 and the first cycle of each dose escalation. Hydration levels should be adjusted according to age and clinical status, and lowered if the subject's cardiovascular status indicates the possibility of volume overload. At the investigator's discretion, allopurinol prophylaxis may be omitted for subjects entering the study with a CR; however subjects must be advised of the need for adequate hydration as outlined above.

Grade 1 TFR may be treated with non-steroidal anti-inflammatory drugs (NSAIDs) (ie, ibuprofen 400-600 mg orally every 4-6 hours as needed) and TFR ≥ Grade 2 should be treated with corticosteroids. Narcotic analgesics may be added as needed for pain control in subjects experiencing ≥ Grade 2 tumor flare.

Subjects will be monitored for TLS and TFR on Days 1, 8 and 15 for cycle 1. Monitoring for TLS and TFR will continue on every 28 days thereafter and as clinically indicated.

It is recommended that subjects receive low dose aspirin (75 mg to 100 mg) as prophylactic anti-thrombotic treatment while on study drug, however the use of aspirin should only be implemented after careful evaluation of the hemorrhagic risk and determination that the subject is at limited risk. The investigator may use other anti-coagulation prophylactic therapies (ie, low-molecular weight (LMW) heparin, warfarin, etc.) at their discretion based on the subjects pre-disposing risk factors for thromboembolism (ie, subjects with a history of a thromboembolic event and/or taking a concomitant medication associated with an increased risk for a thromboembolic event and/or known hypercoagulable state regardless of thromboembolic history).

Aspirin should be interrupted if the platelet count drops below 50,000/μL.

Prophylactic antibiotics should be considered in patients with neutropenia. In addition, subjects who were on prophylactic treatment for infection while on alemtuzumab therapy should continue prophylactic treatment for at least 6 months following the discontinuation of alemtuzumab therapy and can be enrolled into the study while continuing prophylactic therapy. Subjects with an active infection requiring systemic antibiotics and subjects with a systemic infection that has not resolved > 2 months prior to initiating lenalidomide treatment in spite of adequate anti-infective therapy are excluded from entering the study.

Treatment and Dose Modification for Tumor Lysis Syndrome (TLS)

Subjects meeting criteria of laboratory TLS or ≥ Grade 1 TLS according to the Cairo-Bishop definition and grading system should be treated as follows:

- Subjects must be hospitalized for ≥ Grade 1 TLS. For laboratory TLS, hospitalization is left to the investigator's discretion.
- The following should be provided: vigorous hydration and appropriate therapy (ie, rasburicase where available) as needed to reduce hyperuricemia, until correction of electrolyte abnormalities.
- In cases of laboratory TLS and Grade 1 TLS, lenalidomide will be continued at the same dose without interruption or dose reduction. Dose escalation to the next consecutive dose level will be permitted when laboratory TLS is resolved and Grade 1 TLS is resolved to Grade 0.
- Subjects with ≥ Grade 2 TLS will have their dose interrupted and will resume lenalidomide at the next lower dose when electrolyte abnormalities are corrected (ie, Grade 0) as specified in the Dose Modification and Interruption section of the protocol.

If lenalidomide is resumed prior to the start of the subsequent cycle, a chemistry test should be performed every other day for the first week following initiation of lenalidomide.

- When those subjects that have been dose reduced complete two full cycles without meeting criteria for laboratory TLS or ≥ Grade 1 TLS or experiencing toxicities, re-escalation to their maximum dose level or to the next higher dose level is permitted.

A total of 320 subjects will be enrolled (160 subjects/treatment arm) in order to detect a 61.3% improvement (hazard ratio of 0.62) in median OS and PFS in the lenalidomide treatment group compared to placebo-treated subjects with 80% statistical power (see Section 16). Enrollment will close once 320 subjects are randomized or 160 adjudicated PFS events are reached, whichever comes first.

Please refer to Figure 1 for an overall summary of the study design.

Analysis and Reporting:

The final analysis on OS will be performed and reported when 160 subjects have died (ie, when full information necessary to have 80% power for OS is achieved).

Data Monitoring Committee

An external independent Data Monitoring Committee will evaluate safety and efficacy data in an ongoing, periodic manner to assess benefit-to-risk considerations. Since the study will be unblinded, the Data Monitoring Committee will not be utilized beginning with protocol amendment #10. Safety reviews will be performed by Celgene annually for the remainder of the study.

Response Adjudication Committee

An independent Response Adjudication Committee will perform a blinded, independent assessment of response (including the development of PD) prior to the interim analysis database lock. Since the placebo arm is discontinued, the Response Adjudication Committee will not be utilized beginning with protocol amendment #10.

Number of planned subjects: 320 (160 subjects per treatment arm)

Enrollment will close once 320 subjects are randomized or 160 adjudicated PFS events are reached, whichever comes first.

Study Population

Key Inclusion Criteria

1. Must understand and voluntarily sign an informed consent form.
2. Age ≥ 18 years at the time of signing the informed consent form.
3. Must be able to adhere to the study visit schedule and other protocol requirements.
4. Must have a documented diagnosis of B-cell CLL (IWCLL guidelines for the diagnosis and treatment of chronic lymphocytic leukemia, [redacted]
5. Must have been treated with one of the following in first and/or second line:
   - a purine analog-containing regimen
   - a bendamustine-containing regimen
   - an anti-CD20 antibody-containing regimen

- a chlorambucil-containing regimen
- an alemtuzumab-containing regimen (for those subjects with a 17p deletion)

6. Must have achieved a minimum response of partial response (PR, nPR, CRi, CR, and MRD-negative CR) (IWCLL guidelines for the diagnosis and treatment of chronic lymphocytic [redacted] Appendix 22.4) following completion of second-line induction therapy prior to randomization (documentation of response status must be available). Second-line induction therapy must be documented to have been of sufficient duration.
7. Must have completed last cycle of second-line induction no less than 8 weeks (56 days) and no greater than 20 weeks (140 days) prior to randomization.
8. Must have an Eastern Cooperative Oncology Group (ECOG) performance status score of ≤2.
9. Females of childbearing potential (FCBP)† must:
   - Have two negative medically supervised pregnancy tests prior to starting of study therapy. She must agree to ongoing pregnancy testing during the course of the study, and after end of study therapy (see specifics in Appendix 22.6). This applies even if the subject practices complete and continued sexual abstinence.
   - Either commit to continued abstinence from heterosexual contact (which must be reviewed on a monthly basis) or agree to use, and be able to comply with, effective contraception without interruption, 28 days prior to starting study drug, during the study therapy (including dose interruptions), and for 28 days after discontinuation of study therapy, (see specifics in Appendix 22.6).
10. Male subjects must:
    - Commit to continued abstinence from heterosexual contact or agree to use a condom during sexual contact with a FCBP, even if they have had a vasectomy, throughout study drug therapy, during any dose interruption, and after cessation of study therapy (See specifics in Appendix 22.6).
    - Agree to not donate semen during study drug therapy and for a period after end of study drug therapy (see specifics in Appendix 22.6).
11. All subjects must:
    - Have an understanding that the study drug could have a potential teratogenic risk.
    - Agree to abstain from donating blood while taking study drug therapy and following discontinuation of study drug therapy (See specifics in Appendix 22.6).
    - Agree not to share study medication with another person.
    - All subjects must be counseled about pregnancy precautions and risks of fetal exposure (See Appendix 22.6).

† Definition found in appendices

Key Exclusion Criteria

1. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
2. Active infections requiring systemic antibiotics.
3. Systemic infection that has not resolved > 2 months prior to initiating lenalidomide treatment in spite of adequate anti-infective therapy
4. Autologous or allogeneic bone marrow transplant as second-line therapy.
5. Pregnant or lactating females.
6. Systemic treatment for B-cell CLL in the interval between completing the last cycle of second-line induction therapy and randomization.
7. Participation in any clinical study or having taken any investigational therapy for a disease other than CLL within 28 days prior to initiating maintenance therapy.
8. Known presence of alcohol and/or drug abuse.
9. Central nervous system (CNS) involvement as documented by spinal fluid cytology or imaging. Subjects who have signs or symptoms suggestive of leukemic meningitis or a history of leukemic meningitis must have a lumbar puncture procedure performed within two weeks prior to randomization.
10. Prior history of malignancies, other than CLL, unless the subject has been free of the disease for ≥5 years. Exceptions include the following:
    - Basal cell carcinoma of the skin
    - Squamous cell carcinoma of the skin
    - Carcinoma *in situ* of the cervix
    - Carcinoma *in situ* of the breast
    - Incidental histologic finding of prostate cancer (tumor-nodes-metastasis [TNM] stage of T1a or T1b)
11. History of renal failure requiring dialysis.
12. Known Human Immunodeficiency Virus (HIV), active Hepatitis B Virus (HBV) and/or active Hepatitis C Virus (HCV) infection.
13. Prior therapy with lenalidomide.
14. Evidence of TLS per the Cairo-Bishop definition of laboratory TLS (Appendix 22.5) (subjects may be enrolled upon correction of electrolyte abnormalities).
15. Any of the following laboratory abnormalities:
    - Calculated (method of Cockroft-Gault) creatinine clearance of <60 mL/min
    - Absolute neutrophil count (ANC) < 1,000/μL (1.0 X 10^9/L)
    - Platelet count < 50,000/μL (50 X 10^9/L)
    - Serum aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) or alanine transaminase (ALT)/serum glutamate pyruvate transaminase (SGPT) > 3.0 x upper limit of normal (ULN)
    - Serum total bilirubin > 2.0 mg/dL (with the exception of Gilbert's Syndrome)
16. Grade 4 rash due to prior thalidomide treatment.
17. Uncontrolled hyperthyroidism or hypothyroidism.
18. Venous thromboembolism within one year.

19. ≥ Grade-2 neuropathy. 20. Uncontrolled autoimmune hemolytic anemia or thrombocytopenia. 21. Disease transformation (active) (ie, Richter's Syndrome, prolymphocytic leukemia). 22. Known allergy to allopurinol for subjects assessed with PR following their second-line induction therapy. 23. Prisoners. 24. More than 2 prior lines of CLL therapy.
Investigational product, dosage and mode of administration: Celgene Corporation will supply lenalidomide 2.5 mg, 5 mg, and 10 mg capsules for oral administration. Subjects dose reduced to 7.5 mg dose level (as outlined in Section 10.2.1) will receive one 5.0 mg capsule and one 2.5 mg capsule daily. Study drug will be packaged in bottles containing study capsules for 28 days. Subjects currently on lenalidomide treatment will discontinue lenalidomide treatment immediately. Celgene will discontinue supply of lenalidomide as a part of Protocol Amendment #11.

Assessments:

Efficacy:

- Survival/Date of death

Safety:

- Clinical laboratory evaluations
- Pregnancy testing
- [redacted]
- AEs by NCI CTCAE Version 3.0, with modifications recommended by the IWCLL guidelines for the diagnosis and treatment of chronic lymphocytic [redacted] (Appendix 22.4)
- Second primary malignancies will be monitored as events of interest and should be included as part of the assessment of adverse events throughout the course of the study. Investigators are to report any second primary malignancies as serious adverse events regardless of causal relationship to study drug, occurring at any time for the duration of the study, from the time of signing the informed consent up to and including the survival follow-up phase

[redacted]

- [redacted]
- [redacted]

Statistical Analysis:

Overview:

The objective of the statistical analysis will be to compare the efficacy and safety of lenalidomide versus placebo as maintenance therapy in subjects with relapsed or refractory B-cell chronic lymphocytic leukemia (CLL) having achieved PR or better after second-line therapy.

Overall Survival (OS) will be the primary endpoint for the study following protocol amendment #10.

Sample Size:

For OS, a 61.3% improvement in median survival from randomization, from 3 years for placebo to 4.84 years on lenalidomide is considered clinically relevant. The OS distribution is assumed to be exponential with a constant failure (hazard) rate. At the conclusion of the study a two-sided log-rank test with an overall significance level of 0.025 would have 80% power to detect a hazard rate ratio of 0.62. To ensure timely completion of the study, 320 subjects will be enrolled, 160 in each treatment arm. Enrollment will close once 320 subjects are randomized or 160 adjudicated PFS events are reached, whichever comes first.

Demographic, Disposition, Study Medication:

The baseline characteristics of subjects enrolled in each arm will be summarized. An accounting will be made of the study course for all subjects who received study drug for each arm and, in particular, the number of subjects who expired or withdrew during treatment will be specified and reasons for withdrawal categorized.

Efficacy Analysis:

Efficacy analyses will be performed on the intent-to-treat (ITT) population that includes all subjects randomized.

Overall Survival (OS) will be the primary endpoint for the study following protocol amendment #10.

[redacted]

Safety Analysis:

All subjects who receive at least 1 dose of study medication will be included in the safety analyses. AEs, clinical laboratory information, [redacted] will be tabulated and summarized. Subject incidence rates of all AEs (including serious, Grade 3, Grade 4, treatment-related [with and without discontinuation] and events requiring the discontinuation of investigational product), will be tabulated by system class, preferred term, and severity using Medical Dictionary for Regulatory Activities (MedDRA) terms and NCI CTCAE Version 3.0 severity grades with modifications. (Section 10.2.1). Time to first dose reduction will be summarized. The adverse event of infection will also be analyzed according to the grading system as recommended by the IWCLL guidelines for the diagnosis and treatment of CLL [redacted] (Appendix 22.4).

Death and clinically important AEs (including tumor flare, tumor lysis, second primary malignancies, and thrombosis) will also be summarized.

All other measurements will be summarized using means, standard deviations, medians, minimum, and maximum. Graphical displays will be provided where useful in the interpretation of results.

Table 2: Schedule of Assessments

	Maintenance Therapy				After Treatment Discontinuation
Procedure[a]	**Screening ≤ 28 days prior to Day 1**	**Study Day 1**	**Every 28 days (4 weeks)**	**Tx discontinuation**	**Survival Follow-up:[b] Every 24 weeks (+/- 7 days)**
ICF/Inclusion/Exclusion	X	--	--	--	--
Medical history	X	--	--	--	--
Pregnancy test[c]	X[c]	--	X[c]	X[c]	--
Pregnancy and risks counseling[d]	X[d]	X[d]	X[d]	X[d]	--
ECOG Performance Status	X	X	--	X	--
Evaluation of constitutional symptoms	X	X	--	X	--
Physical examination to assess lymphadenopathies, spleen, and liver[e]	X	X	--	X	--
Vital signs including weight[f]	X	X	--	X	--
Hematology[g]	X	X	X	X	--
Chemistry[h]	X	X	X	X	--
Calculated creatinine clearance (method of Cockroft-Gault)	X	--	--	--	--
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Direct Antiglobulin Test (DAT)[j]	X	--	--	--	--
ECG (12 lead)[k]	X	X	--	X	--
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 2 Schedule of Assessments (Continued)

	Maintenance Therapy				After Treatment Discontinuation
Procedure[a]	**Screening ≤28 days prior to Day 1**	**Study Day 1**	**Every 28 days (4 weeks)**	**Tx discontinuation**	**Survival Follow-up:[b] Every 24 weeks (+/- 7 days)**
Tumor lysis monitoring and prophylaxis (allopurinol administration) and tumor flare reaction monitoring[n]	X	X	X	--	--
Study drug administration[o]	--	X	X	--	--
Adverse events[b,p]	X	X	X	X	--
Assessment of Second Primary Malignancies[q]	X	X	X	X	X
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assessment of response[r]	--	--	X	X	--
Survival[b]	--	--	--	--	X

ALC = absolute lymphocyte count; ANC = absolute neutrophil count; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CLL = chronic lymphocytic leukemia; CR = complete response; CRi = complete response with incomplete bone marrow recovery; CRF = case report form; CT = computed tomography; DAT = direct antiglobulin test; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in-situ hybridization; HCT = hematocrit; HGB = hemoglobin; ICF = informed consent form; NK = natural killer; nPR = nodular partial response; PD = progressive disease; PR = partial response; SAE = serious adverse event; WBC = white blood cell; ZAP-70 = Zeta-chain Associated Protein kinase 70

[a] All study procedures should be performed within ± 3 days of the scheduled visit unless otherwise stated.

[b] Subjects who discontinued from the study drug will be followed for survival, subsequent CLL therapies, response to next therapy and progression following next therapy, and second primary malignancies at each of these visits. Subjects will be followed until all subjects in the study have been followed for at least 5 years from last subject randomized, October 2020, (or have died/become lost to follow-up before 5 years).

[c] Females of childbearing potential (FCBP) must have a medically supervised pregnancy test (serum or urine with sensitivity of at least 25 mIU/mL). FCBP must have 2 negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 10 to 14 days prior to the start of study drug and the second pregnancy test must be performed within 24 hours prior to the start of study drug. The patient may not receive study drug until the Investigator has verified that the results of these pregnancy tests are negative (see Appendix 22.6). **For additional information on the frequency and schedule of pregnancy testing, see the document entitles "Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods" in Appendix 22.6. For requirements regarding: 1) counselling and education of patients, including the reading of**

the "Lenalidomide Information Sheet" by the patient; 2) reliable contraception methods; and 3) retention of Risk Management Plan documents concerning the pregnancy prevention program, see Appendix 22.6.

[d] All male and FCBP patients must be counselled about pregnancy precautions and risks of fetal exposure. All patients must also be counselled against sharing study drug and donating blood during and within 28 days of discontinuing study drug (see Appendix 22.6. for frequency).

[e] Physical examination of lymphadenopathies, the spleen and liver will be performed at screening, Study Day 1, and at the treatment discontinuation visit. Lymph node evaluation will record the diameter, in two dimensions, of the largest palpable nodes in each of the following sites: cervical, axillary, supraclavicular, inguinal, and femoral.

[f] Vital signs include: temperature, pulse, blood pressure, weight, and height (height to be measured at baseline only)

[g] Hematology includes WBC, HGB, HCT, platelet count, ANC, and ALC.

[h] Chemistry includes potassium, calcium, phosphorus, creatinine, alkaline phosphatase, total bilirubin, AST/SGOT, ALT/SGPT, and uric acid.

[redacted].

[j] DAT (direct antiglobulin test) will be performed at screening and analyzed at the central laboratory. The DAT test must be repeated if the investigator suspects haemolytic anemia during the course of the study.

[k] ECG will be performed at baseline and at treatment discontinuation and interpreted locally.

[redacted]

[n] Tumor lysis prophylaxis, consisting of oral hydration and allopurinol 300 mg/day, will be administered for **3 days prior to starting treatment** and for at least the first cycle of each dose level. At the investigator's discretion, allopurinol prophylaxis may be omitted for subjects entering the study with a CR; however subjects must be advised of the need for adequate hydration.

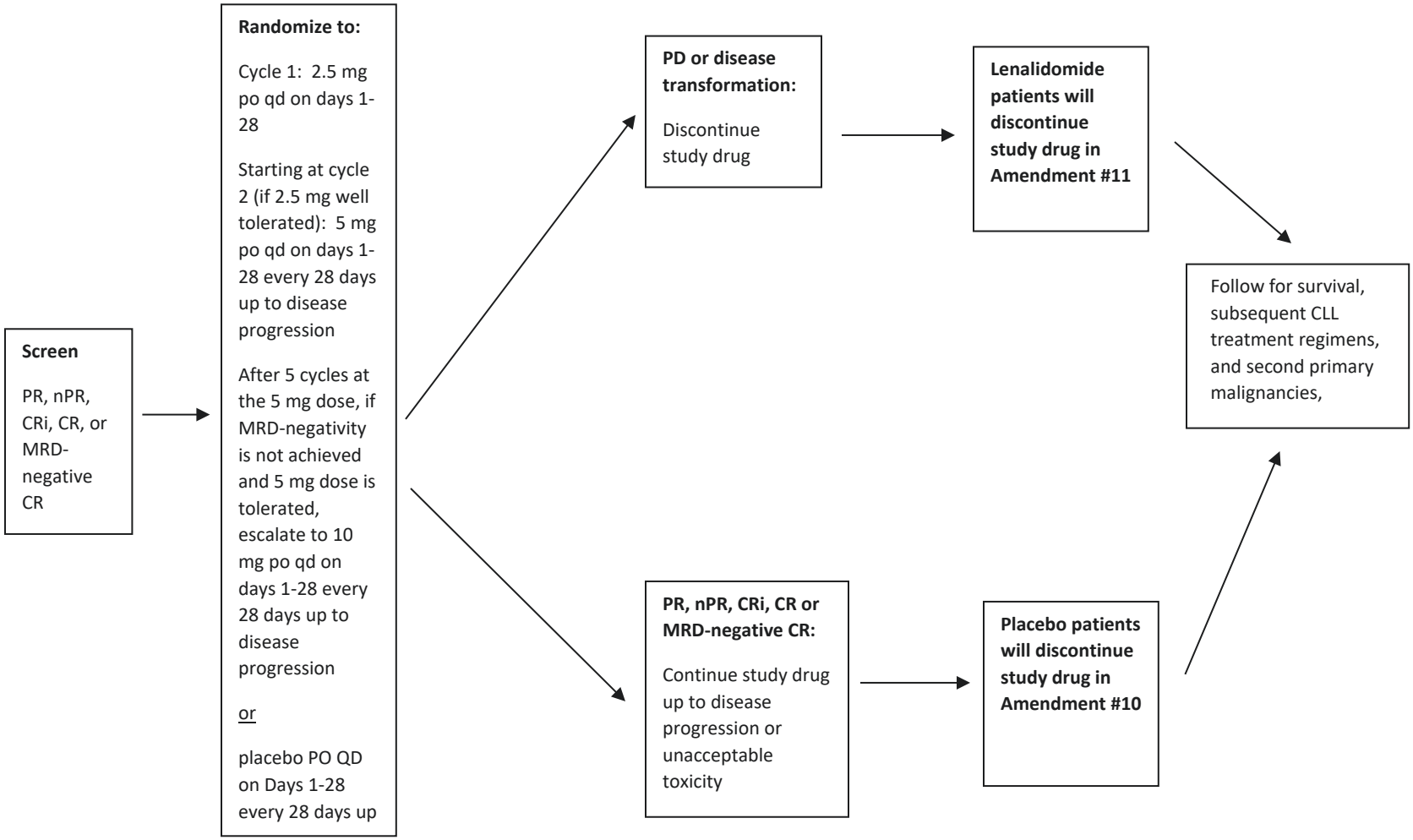
[o] Study drug to be dispensed in 28-day cycles. Subjects should be instructed to return the bottle every 28 days.

[p] Adverse events that lead to study discontinuation should be followed until resolution or stabilization. Serious adverse events should be monitored for 30 days after treatment discontinuation. All SAEs should be followed until resolution or stabilization. Any SAE deemed by the investigator to be related to study drug should be reported and followed until resolution.

[q] Second primary malignancies will be monitored as events of interest and must be reported as serious adverse events. This includes any second primary malignancy, regardless of causal relationship to study drug, occurring at any time for the duration of the study, from the time of signing the informed consent up to and including the survival follow-up period. Subjects will be followed until all subjects in the study have been followed for at least 5 years from randomization (or died/become lost to follow-up before 5 years). Events of second primary malignancy 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 a serious adverse event (eg, any confirmatory histology or cytology results, X-rays, CT scans, etc.).

[r] Investigators to provide assessment of CR, CRi, nPR, PR, and PD based on laboratory, physical exam, and if appropriate bone marrow aspirate/biopsy and CT scan findings. To confirm a complete response, subjects must have maintained no evidence of disease for $\geq$ 8 weeks and partial response must be maintained for $\geq$8 weeks as per the IWCLL guidelines for the diagnosis and treatment of chronic lymphocytic leukemia [redacted]

Figure 1: Schema of Events



CLL= chronic lymphocytic leukemia, CR = complete response, CRi = complete response with incomplete bone marrow recovery, MRD = Minimal residual disease; nPR = nodular partial response, PO = oral, PD = progressive disease, PR = partial response, QD = every day

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 3: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse event
ALC	Absolute lymphocyte count
ALT (SGPT)	Alanine transaminase (serum glutamate pyruvic transaminase)
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST (SGOT)	Aspartate transaminase (serum glutamic oxaloacetic transaminase)
ATC	Anatomic Therapeutic Chemical
β2M	Beta-2 Microglobulin
β –HCG	Beta-human chorionic gonadotropin hormone
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Confidence Interval
CLL	Chronic lymphocytic leukemia
Clb	Chlorambucil
CNS	Central nervous system
CR	Complete response
Cri	Complete response with incomplete bone marrow recovery
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DAT	Direct antiglobulin test
DCF	Data Clarification Form
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency

Abbreviation or Specialist Term	Explanation
EU	European Union

Table 3: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
F	Fludarabine
FC	Fludarabine and Cyclophosphamide
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
FISH	Fluorescence in Situ Hybridization
GClb	Obinutuzumab and Chlorambucil
GCP	Good Clinical Practice
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HGB	Hemoglobin
HCT	Hematocrit
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgVh	Immunoglobulin Heavy-chain Variable-region
IL-6	Interleukin 6
IL-10	Interleukin 10
IMiD	Immunomodulatory drug
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous(ly)
IVRS	Interactive Voice Response System
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
LMW	Low-molecular weight
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or Specialist Term	Explanation
MRD	Minimal residual disease
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events

Table 3: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
NCI-WG	National Cancer Institute Working Group criteria for chronic lymphocytic leukemia
NK cells	Natural killer cells
nPR	Nodular partial response
NSAID	Non-steroidal anti-inflammatory drug
ORR	Overall response rate
OS	Overall Survival
PCR	Pentostatin, cyclophosphamide, and rituximab
PD	Progressive disease
PFS	Progression free survival
PFS2	Progression free survival 2
PR	Partial Response
RClb	Rituxan and Chlorambucil
RIC	Reduced intensity conditioning
SAE	Serious adverse event
SD	Stable disease
SGOT	Serum-Glutamic-Oxaloacetic Transaminase
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reaction
TFR	Tumor flare reaction
TLS	Tumor lysis syndrome
TNF α	Tumor necrosis factor alpha
TNM	Tumor-nodes-metastasis
ULN	Upper limit of normal
US	United States

Abbreviation or Specialist Term	Explanation
VEGF	Vascular endothelial growth factor
VTE	Venous thromboembolism
WBC	White blood cell count
WG	Working Group

Table 3: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
WHO	World Health Organization
ZAP 70	Zeta-Chain-Associated Protein Kinase 70

6. STUDY OBJECTIVES

6.1. Primary Objective

- To compare the efficacy of lenalidomide *versus* placebo maintenance therapy

6.2. Secondary Objective

- To evaluate the safety of lenalidomide *versus* placebo maintenance therapy

7. STUDY ENDPOINTS

7.1. Primary

- Overall Survival (OS)

7.2. Secondary

- Safety [type, frequency, and severity of AEs and relationship of AEs to lenalidomide]
- Progression-Free Survival 2 (PFS2)

8. INVESTIGATIONAL PLAN

8.1. Overall Study Design

CC-5013-CLL-002 is a phase 3, multicenter, randomized, placebo-controlled, parallel-group study that will compare the efficacy and safety of oral lenalidomide maintenance therapy to that of placebo in subjects with B-cell CLL who achieved at least partial response (PR) with second-line therapy. The primary efficacy objective of this study is to demonstrate superiority of lenalidomide over placebo in prolonging OS due to continued therapy, for all subjects, including subjects with or without poor prognostic factors, subjects of various ages and subjects with PR, nodular partial response (nPR), complete response with incomplete bone marrow recovery (CRi), complete response (CR), and minimal residual disease (MRD)-negative CR. All subjects randomized to the lenalidomide arm, including those subjects who do not improve their response (PR, nPR, CRi, or CR) and subjects who do not have the opportunity to improve their response further (MRD-negative CR) will be treated up to disease progression with the objective to demonstrate prolongation of OS.

Amendment #11:

Subjects currently on lenalidomide treatment will discontinue lenalidomide treatment immediately and complete the Treatment Discontinuation assessment. The subjects will then transition to the survival follow-up period.

Eligible subjects must have been treated with a purine analog-, a bendamustine-, an anti-CD20 antibody-, or a chlorambucil-based regimen in first and/or second line and must have achieved at least PR to second-line induction therapy of sufficient duration. Alemtuzumab- containing regimens will also be allowed for those patients with 17p deletion. Subjects who achieve stable disease (SD) only or who develop progressive disease (PD) at any time during induction therapy will not be eligible for participation in this study.

Approximately, three hundred twenty (320) subjects with PR, nPR, CRi, CR or MRD-negative CR will be enrolled and randomized (1:1) into two arms: placebo daily or lenalidomide 2.5 mg daily on days 1-28 of the first cycle. If the 2.5 mg dose level is well tolerated, escalation to 5 mg daily on days 1-28 of each 28-day cycle is permitted starting with the second cycle. If a subject develops a Grade 1 or 2 adverse event, the drug may be interrupted until resolution, however the subject must complete one full cycle at the 2.5 mg dose level prior to escalation to the 5 mg dose level. For those subjects who tolerate the 5 mg dose without unacceptable toxicity, escalation to 10 mg daily on days 1-28 of each 28-day cycle after 5 continuous cycles at 5 mg will be permitted. Each treatment arm will be stratified according to 1) the response to second-line induction therapy (PR, nPR, CRi or CR versus MRD-negative CR); 2) age ($\leq$ 70 versus > 70 years); and 3) presence of at least one of the following poor prognostic factors: 11q deletion, 17p deletion, unmutated IgV_H or $\beta 2M$ > 4.0 mg/L (Yes versus No versus Unknown).

The subjects randomized to the lenalidomide treatment will continue to receive lenalidomide up to PD. For those subjects who discontinue therapy for reasons other than PD (ie, unacceptable toxicity) they will transition to the survival follow-up period.

Subjects who discontinued from the study drug will be followed every 24 weeks for survival, subsequent CLL therapies, response to next therapy and progression following next therapy, and

second primary malignancies. Subjects will be followed until all subjects in the study have been followed for at least 5 years from the last randomization, October 2020, (or have died/become lost to follow up before 5 years).

Screening:

Potential study subjects will be screened for protocol eligibility within 28 days prior to randomization as outlined in Table 2. Please refer to Figure 1.

During the screening process for potentially protocol-eligible subjects, complete blood counts (CBCs), serum chemistries, thyroid function tests, quantitative immunoglobulin tests, a 12-lead electrocardiogram (ECG), physical exam to assess lymphadenopathies, the spleen and the liver, vital signs (with weight), Eastern Cooperative Oncology Group (ECOG) performance status, and evaluation of constitutional symptoms will be performed.

Bone marrow biopsies and aspirates are to be performed on all subjects at screening. A central review of the bone marrow aspirate and biopsy specimens will be performed to confirm disease status. Subjects who develop PD during screening will not be eligible to enroll into this study. Peripheral blood will be sent to a central laboratory for flow cytometry for all subjects for disease diagnosis confirmation (by immunophenotyping), to perform immune cell (NK and T cell) analyses and for subjects entering the study with a CR for determination of MRD status. If peripheral blood is MRD negative, a bone marrow flow cytometry will be implemented. If subjects enter the study with MRD negativity, the disease diagnosis will be confirmed based on prior flow cytometry (documentation needed).

A peripheral blood sample for a direct antiglobulin test (DAT) will be collected and analyzed at a central laboratory.

Before randomization, subjects will be tested for cytogenetics by FISH, IgV_H mutational status, and β2M. The β2M test will be performed during screening using a peripheral blood sample and analyzed at a central laboratory.

FISH and IgV_H testing will be performed prior to second line, during second line, in the interval between second-line therapy and screening or during the screening period using a peripheral blood sample. Because test results cannot be obtained during screening or between second line and screening in some subjects who achieve a good response due to the limited number of remaining CLL cells, we recommend conducting the FISH and IgV_H tests preferably prior to second line or during second line.

Samples for FISH and IgV_H will be analyzed at a central laboratory.

If tests do not yield results, subjects can be randomized and stratified based on historical data.

Those subjects for whom results were not obtainable pre-randomization and for whom no historical data were available will be enrolled and grouped separately.

An additional peripheral blood sample will be collected at baseline and stored at -70° at a central laboratory until the completion of the study; subjects will be re-consented if additional testing is to be performed.

Computed tomography (CT) scans of the chest, abdomen, and pelvis will be performed at baseline for all subjects to document the subject's status (PR or CR).

If, during the screening period, the subject has a correctable event that prevents randomization and the event cannot be corrected within the 28 day screening period, the subject may be re-screened; however, the CT scans and bone marrow aspirate and biopsy will not need to be repeated if those tests were implemented within 56 days prior to randomization and the subject's clinical status remains the same.

Females of childbearing potential (FCBP) must have two negative pregnancy tests performed at the study site prior to initiating lenalidomide therapy. The first pregnancy test will be performed within 10-14 days prior to randomization and the second test within 24 hours prior to starting study drug. FCBP must agree to birth control requirements as outlined in Appendix 22.6 during the following time periods related to this study: 1) for at least 28 days before starting study drug; 2) while participating in the study; and 3) at least 28 days after the treatment discontinuation visit. FCBP must be referred to a qualified provider of contraceptive methods, if needed. Males must commit to continued abstinence from heterosexual contact or agree to use appropriate contraceptive methods during any sexual contact with FCBP during study participation and for at least 28 days following the treatment discontinuation visit as outlined in Appendix 22.6. Male subjects must agree to abstain from donating blood, semen or sperm during study participation and for at least 28 days after the treatment discontinuation visit. Subjects must be counseled about pregnancy precautions and the potential risk of fetal exposure.

Randomization:

Randomization must occur no less than 8 weeks (56 days) and no greater than 20 weeks (140 days) from the last day of the last cycle of second-line induction therapy received by the subject in order for the subject to be eligible for enrollment into this study. Subjects meeting all eligibility criteria will be randomized (1:1) in a double-blind fashion to receive either lenalidomide or placebo. The randomization procedure will be accomplished by a validated interactive voice response system (IVRS) (see Section 10.1.1). Subjects will be stratified at randomization by: 1) their response to second-line induction therapy (PR, nPR, CRi or CR versus MRD-negative CR); 2) age (≤ 70 versus > 70 years); and 3) presence of at least one of the following poor prognostic factors: 11q deletion, 17p deletion, unmutated IgV_H or β2M > 4.0 mg/L (Yes versus No versus Unknown).

Maintenance Therapy:

Study treatment for each subject begins on the same day the subject undergoes randomization. Lenalidomide is administered orally. Subjects will receive lenalidomide 2.5 mg once daily on Days 1 through 28 of the first 28-day cycle. If the 2.5 mg dose is well tolerated (subject does not experience any Grade 3 or 4 study drug-related toxicities or any other toxicity [Grade 1 or 2] found to be unacceptable by the investigator or the subject), subjects should be escalated starting at the second cycle to 5 mg once daily on Days 1 through 28 of each 28-day cycle up to disease progression. If a subject develops a Grade 1 or 2 adverse event, the drug may be interrupted until resolution, however the subject must complete one full cycle at the 2.5 mg dose level prior to escalation to the 5 mg dose level.

Subjects who complete 5 continuous cycles at the 5 mg dose level without experiencing any Grade 3 or 4 study drug-related toxicities and without experiencing any other toxicity (Grade 1 or 2) found to be unacceptable by the investigator may be escalated to 10 mg once daily on Days 1 through 28 of each 28-day cycle up to disease progression.

Dose de-escalation to 7.5 mg from 10 mg and to 5 mg from 7.5 mg and to 2.5 mg from 5 mg and to 2.5 mg every other day from 2.5 mg will be permitted for those subjects who experience a Grade 3 or 4 study drug-related toxicity or any other Grade 1 or 2 toxicity found to be unacceptable by the investigator or subject.

Dose interruptions are also permitted for Grade 1 or 2 adverse events at the investigator's discretion. A guideline for the reduction of the dose of lenalidomide for dose-limiting toxicity (DLT) is provided (see Section 10.2.1).

Dose re-escalation is permitted if the subject is able to complete 2 full cycles at the reduced dose level without experiencing a DLT or other toxicity deemed to be unacceptable by the investigator or subject. In the event the dose reduction is implemented due to Grade 4 neutropenia, subjects may be re-escalated after one full cycle at the lower dose level if the neutropenia resolves to a Grade 2 or better by the end of the cycle and no other DLT is observed. If that dose level is again not tolerated, the subject should be de-escalated to the dose below and remain at that tolerated dose level for the rest of the study.

Study visits and serial measurements of safety and efficacy will be performed as outlined in Table 2.

Females of childbearing potential must have a pregnancy test (conducted by the study site) within 24 hours prior to starting study drug; the subject may not receive study drug until the Investigator has verified that the pregnancy test is negative. Pregnancy testing for FCBP will continue throughout the study as outlined in Table 2 and Appendix 22.6.

Counseling regarding blood, eggs and ovum donation, and contraceptive use and the potential risks of fetal exposure should be performed as outlined in Appendix 22.6.

FCBP should be monitored during the course of the study and after the end of study therapy to:

- Ensure that pregnancy tests are performed during the course of the study and after end of study therapy and are negative (see specifics in Appendix 22.6).
- Ensure the subject continues to practice abstinence or remains on adequate contraception (see specifics in Appendix 22.6).

If a FCBP becomes pregnant, treatment should be stopped and the subject referred to the appropriate physician.

Male subjects should be monitored during the course of the study and after the end of study therapy to:

- Ensure they commit to continued abstinence from heterosexual contact or continue to use a condom during sexual contact with a FCBP.
- If a female partner of a male subject becomes pregnant she should be referred to the appropriate physician.

CBCs will be monitored on Days 1, 8, and 15 of cycle 1, on Day 1 of each cycle thereafter, and at the treatment discontinuation visit. In the event of Grade 4 hematologic toxicity, monitoring of CBCs will continue weekly until resolution to grade 3 or better. It is recommended to utilize myeloid and erythroid growth factors as per the American Society of Clinical Oncology (ASCO)

guidelines. The use of myeloid growth factors is encouraged when the absolute neutrophil count (ANC) is less than 1,000/μL.

If a subject develops Grade 4 neutropenia or thrombocytopenia, the drug will be withheld until the toxicity has recovered to Grade 3 or better. The drug may then be restarted at one dose level lower. If the treatment has been withheld and the next cycle is delayed beyond 29 days after day 1 of the prior treatment cycle, then day 1 of the next treatment cycle will be defined as the first day that the treatment is resumed.

Serum chemistries will be performed on Days 1, 8, and 15 of cycle 1, on Day 1 of each cycle thereafter, and at the treatment discontinuation visit.

Scheduled laboratory studies (CBCs, chemistries) will be sent to the site's local laboratory for analysis purposes.

The DAT test must be repeated if the investigator suspects haemolytic anemia and will be analysed centrally during the course of the study.

ECOG Performance Status will be measured at the treatment discontinuation visit.

Evaluation of constitutional symptoms will be performed at the treatment discontinuation visit.

Vitals signs will be monitored at the treatment discontinuation visit. A physical examination to assess in particular lymphadenopathies, spleen and liver will be performed at the treatment discontinuation visit.

An ECG will be performed at the treatment discontinuation visit.

Investigators will assess subjects for response every 28 days and at the treatment discontinuation visit. Investigators will provide an assessment of CR (MRD-negative or MRD-positive), CRi, nPR, PR, and PD based on laboratory, physical exam, and if appropriate local assessments for CT scan findings, flow cytometry and bone marrow aspirate and biopsy. To confirm a CR, subjects must have maintained no evidence of disease for ≥ 8 weeks and PR must be maintained for ≥ 8 weeks as per the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) guidelines for the diagnosis and treatment of chronic lymphocytic leukemia (Hallek, 2008).

FCBP must have a pregnancy test at the treatment discontinuation visit.

Subjects will receive study maintenance therapy until PD develops; any disease transformation will need to be documented by lymph node biopsies for Richter's syndrome and percent of peripheral blood or bone marrow prolymphocytes for prolymphocytic leukemia. Progressive disease is characterized by at least one of the following:

- Lymphadenopathy. Progression of lymphadenopathy discovered by physical examination. Disease progression occurs if one of the following events is observed:
  - Appearance of any new lesion such as enlarged lymph nodes (> 1.5 cm), splenomegaly, hepatomegaly or other organ infiltrates.
  - An increase by 50% or more in greatest determined diameter of any previous site.
- An increase in the previously noted enlargement of the liver or spleen size by 50% or more or the de novo appearance of hepatomegaly or splenomegaly.

- An increase in the number of blood lymphocytes by 50% or more with at least 5,000 B lymphocytes per μL.
- Transformation to a more aggressive histology (eg, Richter's syndrome). Whenever possible, this diagnosis should be established by lymph node biopsy.
- Occurrence of cytopenia (neutropenia, anemia or thrombocytopenia) attributable to CLL.
- During therapy: cytopenias may occur as a side effect of many therapies and should be assessed according to Table 4. During therapy, cytopenias cannot be used to define disease progression.
- Post treatment: The progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of hemoglobin levels by more than 2 g/dL or to less than 10 g/dL, or by a decrease of platelet counts by more than 50% or to less than 100,000/μL, which occurs at least 3 months after treatment, defines disease progression, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells.

Prophylaxis for TLS, thromboembolism and infection and treatment of tumor flare reaction (TFR):

TLS prophylaxis, comprising of oral hydration and allopurinol 300 mg/day will be initiated 3 days prior to starting maintenance therapy and for a minimum of the first treatment cycle at each dose level for those subjects entering the study with a PR to their second-line induction therapy. Subjects with a known allergy to allopurinol with a response of PR will be excluded from the study. Please refer to Section 10.2.1 for further guidance on allopurinol modification in the event of an adverse event. If a subject is taking allopurinol for a condition other than for TLS prophylaxis, the subject should be continued on the allopurinol prescribed by their physician and the dose titrated to 300 mg/day. If, at any time, the allopurinol being taken for reasons other than TLS prophylaxis is discontinued and prophylaxis is still required per protocol, the subject should be administered commercial allopurinol. To maintain fluid intake, subjects must be instructed to drink 8 to 10 eight ounce (240 mL) glasses of water each day for the first 14 days of cycle 1 and the first cycle of each dose escalation. Hydration levels should be adjusted according to age and clinical status, and lowered if the subject's cardiovascular status indicates the possibility of volume overload. At the investigator's discretion, allopurinol prophylaxis may be omitted for subjects entering the study with a CR; however subjects must be advised of the need for adequate hydration as outlined above.

Grade 1 TFR may be treated with non-steroidal anti-inflammatory drug (NSAIDs) (ie, ibuprofen 400-600 mg orally every 4-6 hours as needed) and TFR ≥ Grade 2 should be treated with corticosteroids. Narcotic analgesics may be added as needed for pain control in subjects experiencing ≥ Grade 2 tumor flare.

Subjects will be monitored for TLS and TFR on Days 1, 8, and 15 for cycle 1 and the first cycle of each dose escalation. Monitoring for TLS and TFR will continue on Days 1 and 15 for the second cycle of each dose level, at least every 28 days thereafter, and as clinically indicated.

It is recommended that subjects receive low dose aspirin (75 mg to 100 mg) as prophylactic anti-thrombotic treatment while on study drug, however the use of aspirin should only be

implemented after careful evaluation of the hemorrhagic risk and determination that the subject is at limited risk. The investigator may use other anti-coagulation prophylactic therapies (ie, low-molecular weight (LMW) heparin, warfarin, etc.) at their discretion based on the subjects pre-disposing risk factors for thromboembolism (ie, subjects with a history of a thromboembolic event and/or taking a concomitant medication associated with an increased risk for a thromboembolic event and/or known hypercoagulable state regardless of thromboembolic history).

Aspirin should be interrupted if the platelet count drops below 50,000/μL.

Prophylactic antibiotics should be considered in patients with neutropenia. In addition, subjects who were on prophylactic treatment for infection while on alemtuzumab therapy should continue prophylactic treatment for at least 6 months following the discontinuation of alemtuzumab therapy and can be enrolled into the study while continuing prophylactic therapy. Subjects with an active infection requiring systemic antibiotics and subjects with a systemic infection that has not resolved > 2 months prior to initiating lenalidomide treatment in spite of adequate anti-infective therapy are excluded from entering the study.

Treatment and Dose Modification for Tumor Lysis Syndrome (TLS):

Subjects meeting criteria of laboratory TLS or ≥ Grade 1 TLS according to the Cairo-Bishop definition and grading system should be treated as follows:

- Subjects must be hospitalized for ≥ Grade 1 TLS. For laboratory TLS, hospitalization is left to the investigator's discretion.
- The following should be provided: vigorous hydration and appropriate therapy (ie, rasburicase where available) therapy as needed to reduce hyperuricemia, until correction of electrolyte abnormalities.
- In cases of laboratory TLS and Grade 1 TLS, lenalidomide will be continued at the same dose without interruption or dose reduction. Dose escalation to the next consecutive dose level will be permitted when laboratory TLS is resolved and Grade 1 TLS is resolved to Grade 0.
- Subjects with ≥ Grade 2 TLS will have their dose interrupted and will resume lenalidomide at the next lower dose when electrolyte abnormalities are corrected (ie, Grade 0) as specified in the Dose Modification and Interruption section of the protocol. If lenalidomide is resumed prior to the start of the subsequent cycle, a chemistry test should be performed every other day for the first week following initiation of lenalidomide.
- When those subjects that have been dose reduced complete two full cycles without meeting criteria for laboratory TLS or ≥ Grade 1 TLS or experiencing toxicities, re-escalation to their maximum dose level or to the next higher dose level is permitted.

The severity of AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0 with modifications. The severity of TLS AEs will be graded according to the Cairo-Bishop grading system.

Amendment #11:

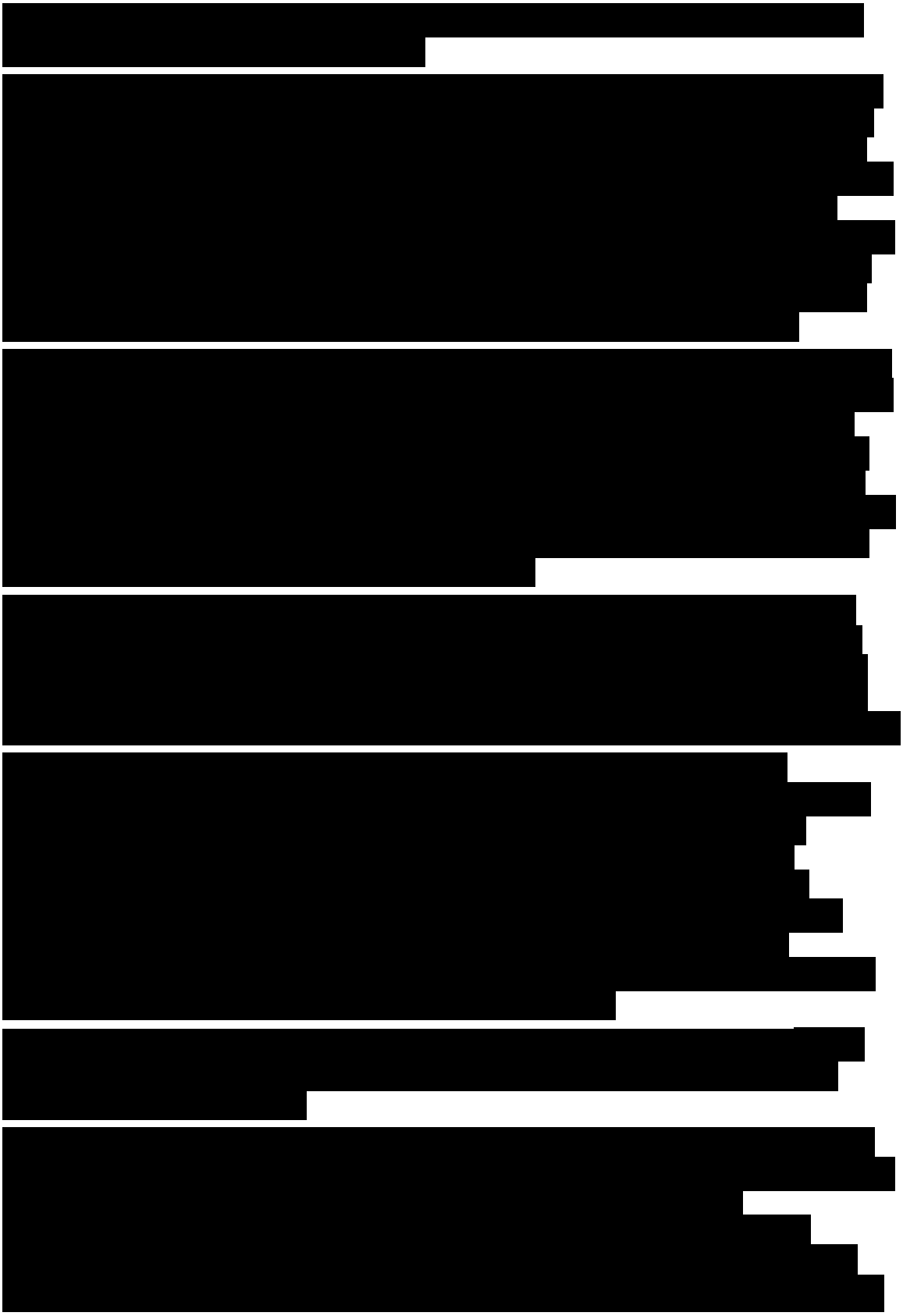
Subjects currently on lenalidomide treatment will discontinue lenalidomide treatment immediately and complete the Treatment Discontinuation assessment. The subjects will then transition to the survival follow-up period.

After Study Discontinuation:

Upon discontinuation of study drug, subjects will be followed every 24 weeks for survival, information on other CLL treatments, response to next therapy and progression following next therapy, and second primary malignancies (reported as SAEs). Subjects will be followed until all subjects in the study have been followed for at least 5 years from the last randomization, October 2020 (or have died/become lost to follow-up before 5 years).

FCBP with regular menstrual cycles discontinued from treatment must have a pregnancy test on day 28 after the treatment discontinuation visit. FCBP with irregular cycles discontinued from treatment must have a pregnancy test on days 14 and 28 after the treatment discontinuation visit.

SAEs will continue to be collected for the first 30 days after the treatment discontinuation visit. Following 30 days post the treatment discontinuation visit, only SAEs related to maintenance therapy will be collected for the study duration. Second primary malignancies must be reported as SAEs. This includes any second primary malignancy, regardless of causal relationship to study medication, occurring at any time for the duration of the study, from the time of signing the informed consent up to and including progression free follow-up and survival follow-up.



9. STUDY POPULATION

9.1. Subject Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Must understand and voluntarily sign an informed consent form.
2. Must be ≥18 years at the time of signing the informed consent form.
3. Must be able to adhere to the study visit schedule and other protocol requirements.
4. Must have a documented diagnosis of B-cell CLL (IWCLL guidelines for the diagnosis and treatment of chronic lymphocytic leukemia [redacted]).
5. Must have been treated with one of the following in first and/or second line:
   - a purine analog-containing regimen
   - a bendamustine-containing regimen
   - an anti-CD20 antibody-containing regimen
   - a chlorambucil-containing regimen
   - an alemtuzumab-containing regimen (for those subjects with a 17p deletion)
6. Must have achieved a minimum response of partial response (PR, nPR, CRi, CR, and MRD-negative CR) (IWCLL guidelines for the diagnosis and treatment of chronic lymphocytic leukemia [redacted] Appendix 22.4) following completion of second-line induction therapy prior to randomization (documentation of response status must be available). Second-line induction therapy must be documented to have been of sufficient duration.
7. Must have completed last cycle of second-line induction no less than 8 weeks (56 days) and no greater than 20 weeks (140 days) prior to randomization.
8. Must have an ECOG performance status score of ≤2.
9. Females of childbearing potential (FCBP)[†] must:
   - Have two negative medically supervised pregnancy tests prior to starting of study therapy. She must agree to ongoing pregnancy testing during the course of the study, and after end of study therapy. (see specifics in Appendix 22.6). This applies even if the subject practices complete and continued sexual abstinence.

[†] Definition found in appendices

- Either commit to continued abstinence from heterosexual contact (which must be reviewed on a monthly basis) or agree to use, and be able to comply with, effective contraception without interruption, 28 days prior to starting study drug, during the study therapy (including dose interruptions), and for 28 days after discontinuation of study therapy (see specifics in Appendix 22.6).

10. Male subjects must:
    - Commit to continued abstinence from heterosexual contact or agree to use a condom during sexual contact with a FCBP, even if they have had a vasectomy, throughout study drug therapy, during any dose interruption and after cessation of study therapy. (see specifics in Appendix 22.6)
    - Agree to not donate semen during study drug therapy and for a period after end of study drug therapy (see specifics in Appendix 22.6).
11. All subjects must:
    - Have an understanding that the study drug could have a potential teratogenic risk.
    - Agree to abstain from donating blood while taking study drug therapy and following discontinuation of study drug therapy. (See specifics in Appendix 22.6)
    - Agree not to share study medication with another person.
    - All subjects must be counseled about pregnancy precautions and risks of fetal exposure. See Appendix 22.6.

9.2. Subject Exclusion Criteria

1. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
2. Active infections requiring systemic antibiotics.
3. Systemic infection that has not resolved > 2 months prior to initiating lenalidomide treatment in spite of adequate anti-infective therapy
4. Autologous or allogeneic bone marrow transplant as second-line therapy.
5. Pregnant or lactating females.
6. Systemic treatment for B-cell CLL in the interval between completing the last cycle of second-line induction therapy and randomization.
7. Participation in any clinical study or having taken any investigational therapy for a disease other than CLL within 28 days prior to initiating maintenance therapy.
8. Known presence of alcohol and/or drug abuse.
9. Central nervous system involvement as documented by spinal fluid cytology or imaging. Subjects who have signs or symptoms suggestive of leukemic meningitis or a history of leukemic meningitis must have a lumbar puncture procedure performed within two weeks prior to randomization.

10. Prior history of malignancies, other than CLL, unless the subject has been free of the disease for ≥5 years. Exceptions include the following:
    - Basal cell carcinoma of the skin
    - Squamous cell carcinoma of the skin
    - Carcinoma *in situ* of the cervix
    - Carcinoma *in situ* of the breast
    - Incidental histologic finding of prostate cancer (tumor-nodes-metastasis [TNM] stage of T1a or T1b)
11. History of renal failure requiring dialysis.
12. Known Human Immunodeficiency Virus (HIV), active Hepatitis B Virus (HBV), and/or active Hepatitis C Virus (HCV) infection.
13. Prior therapy with lenalidomide.
14. Evidence of TLS per the Cairo-Bishop definition of laboratory TLS (Appendix 22.5) (subjects may be enrolled upon correction of electrolyte abnormalities).
15. Any of the following laboratory abnormalities:
    - Calculated (method of Cockroft-Gault) creatinine clearance <60 mL/min.
    - Absolute neutrophil count (ANC) <1,000/μL (1.0 X 10^9/L)
    - Platelet count <50,000/μL (50 X 10^9/L)
    - Serum aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) or alanine transaminase (ALT)/serum glutamate pyruvate transaminase (SGPT) > 3.0 x upper limit of normal (ULN)
    - Serum total bilirubin >2.0 mg/dL (with the exception of Gilbert's Syndrome)
16. Grade 4 rash due to prior thalidomide treatment
17. Uncontrolled hyperthyroidism or hypothyroidism
18. Venous thromboembolism within one year
19. ≥Grade-2 neuropathy
20. Uncontrolled autoimmune hemolytic anemia or thrombocytopenia
21. Disease transformation (active) (ie, Richter's Syndrome, prolymphocytic leukemia)
22. Known allergy to allopurinol for subjects assessed with PR following their second-line induction therapy.
23. Prisoners.
24. More than 2 prior lines of CLL therapy.

10. DESCRIPTION OF TREATMENT

10.1. Description of Study Drug

Celgene Corporation will supply lenalidomide 2.5 mg, 5 mg, and 10 mg capsules for oral administration. Subjects dose reduced to 7.5 mg dose level (as outlined in Section 10.2.1) will receive one 5.0 mg capsule and one 2.5 mg capsule daily.

Study drug will be packaged in bottles containing study capsules for 28 days. Subjects assigned to active treatment will receive 28 days of active drug (with the exception of those subjects de-escalated to 2.5 mg every other day).

Celgene Corporation will no longer supply blinded allopurinol 300 mg and matching placebo (Amendment #10).

Subjects currently on lenalidomide treatment will discontinue lenalidomide treatment immediately. Celgene Corporation will no longer supply lenalidomide (Amendment #11).

10.1.1. Randomization

Randomization will be accomplished by an IVRS to ensure timely registration and randomization. Designated research personnel at the investigational sites will be assigned password protected, coded identification numbers, which gives them authorization to call into the IVRS to enroll subjects. The system will present a menu of questions by which the research personnel will identify the subject and confirm eligibility. When all questions have been answered, including questions regarding the results of pregnancy tests for FCBP, the IVRS will assign a subject number and study drug to the eligible subject. IVRS will fax a confirmation of registration and drug assignment for each subject to the site and Celgene. Subjects will be randomized (1:1) to receive lenalidomide or placebo. Subjects will be stratified at randomization by: 1) their response to second-line induction therapy (PR, nPR, CRi or CR versus MRD-negative CR); 2) age (≤ 70 versus > 70 years); and 3) presence of at least one of the following poor prognostic factors: 11q deletion, 17p deletion, unmutated IgV_H, or β2M > 4.0 mg/L (Yes versus No versus Unknown).

Site staff are to contact Celgene at each visit for study drug assignment, to register dose reductions or escalations, and at discontinuation from treatment. Confirmation of each call will be faxed to the site.

10.2. Treatment Assignments

Lenalidomide

Oral lenalidomide 2.5 mg capsule once daily on Days 1 through 28 of the first 28-day cycle. If the 2.5 mg dose is well tolerated, subjects should be escalated starting at the second cycle to 5 mg capsule once daily on Days 1 through 28 of each 28-day cycle to disease progression. If a subject develops a Grade 1 or 2 adverse event, the drug may be interrupted until resolution, however the subject must complete one full cycle at the 2.5 mg dose level prior to escalation to the 5 mg dose level.

Following 5 continuous cycles at the 5 mg dose level, subjects who are tolerating the 5 mg dose level may be escalated to 10.0 mg once daily on days 1 through 28 of each 28-day cycle up to disease progression.

Amendment #11:

Subjects currently on lenalidomide treatment will discontinue lenalidomide treatment immediately and complete the Treatment Discontinuation assessment. The subjects will then transition to the survival follow-up period.

10.2.1. Dose Modification or Interruption

Subjects will be evaluated for AEs at each visit with the NCI CTCAE (Version 3.0) used as a guide for the grading of severity with the exceptions recommended by the IWCLL guidelines for the diagnosis and treatment of chronic lymphocytic leukemia [redacted] as listed below*:

Table 4: Grading Scale for Hematological Toxicity in CLL Studies

Grade#	Decrease in Platelets* or Hb° (nadir) From Pretreatment value (%)	Absolute neutrophil count/µL@ (nadir)
0	No change to 10%	≥ 2,000
1	11% - 24%	≥1,500 and < 2,000
2	25% - 49%	≥1,000 and < 1,500
3	50% - 74%	≥ 500 and < 1,000
4	≥ 75%	< 500

* Platelet counts must be below normal levels for grades 1-4. If, at any level of decrease the platelet count is <20,000/µL, this will be considered grade 4 toxicity, unless a severe or life-threatening decrease in the initial platelet count (eg, 20,000/µL) was present pretreatment, in which case the patient is not evaluable for toxicity referable to platelet counts.

° Hb levels must be below normal levels for grades 1-4. Baseline and subsequent Hb determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity, but should be documented.

Grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, fatal. Death occurring as a result of toxicity at any level of decrease from pretreatment will be recorded as grade 5.

@ If the absolute neutrophil count (ANC) reaches less than 1,000/µL, it should be judged to be grade 3 toxicity. Other decreases in the white blood cell count, or in circulating granulocytes, are not to be considered, since a decrease in the white blood cell count is a desired therapeutic end point. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. The use of G-CSF is irrelevant for the grading toxicity, but should be documented.

In addition, TLS will be graded as specified by the Cairo-Bishop grading system (Appendix 22.5). Subjects meeting criteria of laboratory TLS or ≥ Grade 1 TLS, will be hospitalized (per investigator's discretion for laboratory TLS), provided with vigorous intravenous hydration and appropriate therapy (ie, rasburicase where available) as needed to reduce hyperuricemia, until correction of electrolyte abnormalities. In the case of laboratory TLS and Grade 1 TLS, lenalidomide will be continued at the same dose without interruption or dose reduction. Subjects with ≥ Grade 2 TLS, will have their dose interrupted and will resume lenalidomide at the next lower dose level when electrolyte abnormalities are corrected (ie, Grade 0). If lenalidomide is

resumed prior to the start of the subsequent cycle, chemistry tests should be performed every other day for the first week following initiation of lenalidomide.

If a subject develops toxicity (Table 6), the dose may be reduced as outlined in Table 5.

Table 5: Dose Reduction Steps

Lenalidomide Dose	2.5 mg every day x 28 days of a 28-day cycle	5 mg every day x 28 days of a 28-day cycle	10 mg every day x 28 days of a 28-day cycle
Dose Reduction – 1	2.5 mg every other day x 28 days of a 28-day cycle	2.5 mg every day x 28 days of a 28-day cycle	7.5 mg every day x 28 days of a 28- day cycle
Dose Reduction – 2	n/a	2.5 mg every other day x 28 days of a 28-day cycle	5 mg every day x 28 days of a 28- day cycle
Dose Reduction – 3	n/a	n/a	2.5 mg every day x 28 days of a 28- day cycle
Dose Reduction – 4	n/a	n/a	2.5 mg every other day x 28 days of a 28-day cycle

Subjects experiencing a ≥ Grade 3 non-hematologic AE will have their study drug held until resolution of the AE as described in Table 6: Dose Reduction and Modification Guidelines. Subjects with a hematologic AE will modify study drug dosing as outlined in Table 6.

Subjects who cannot tolerate 2.5 mg every other day x 28 days of a 28-day cycle are to be discontinued from study drug and followed for survival as outlined in Table 2.

Table 6: Dose Reduction and Modification Guidelines

NCI CTCAE Toxicity Grade	Action
Neutropenia ANC < 400/uL	• Interrupt study drug therapy • Resume study drug (decrease one dose level) when ANC recovers to ≥ 500/uL
Thrombocytopenia < 20,000/uL	• Interrupt study drug therapy • Resume study drug (decrease one dose level) when platelet count recovers to ≥ 25,000/uL
Syndromes	
Tumor Flare Grade 3 or 4	• Interrupt study drug therapy and initiate therapy with NSAIDs, narcotic analgesics or prednisone • Resume study drug (decrease one dose level) when symptoms resolve to ≤ Grade 2
Desquamating (blistering) rash	• Discontinue study drug
Non- desquamating rash Grade 3	• Interrupt study drug therapy.

NCI CTCAE Toxicity Grade	Action
Grade 4	• Resume study drug when the rash resolves to ≤ Grade 1 (decrease one dose level) • Discontinue study drug

Table 6: Dose Reduction and Modification Guidelines (Continued)

NCI CTCAE Toxicity Grade	Action
Neuropathy Grade 3 Grade 4	 • If Grade 3, interrupt study drug therapy. • Resume study drug when the neuropathy resolves to ≤ Grade 1 (decrease one dose level) • If Grade 4, discontinue study drug
Venous thrombosis/embolism ≥ Grade 3	• Hold (interrupt) dose and start anticoagulation; • Resume study drug when adequately anticoagulated (maintain dose level).
Hyperthyroidism or hypothyroidism	• Interrupt study drug and initiate appropriate medical therapy. • Resume study drug when appropriately controlled (maintain dose level).
Serum Creatinine Grade 1 **It is possible for subjects entering the study with a creatinine clearance ≥ 60 ml/min and a serum creatinine at the upper limit of normal to show slight fluctuations of the serum creatinine above the upper limit of normal. It is left at the investigator's discretion to measure the creatinine clearance for those subjects to evaluate whether a dose adjustment is needed.	 • Interrupt study drug • Evaluate subject weekly x 3 weeks • If during those 3 weeks, the creatinine level worsened at any time to > Grade 1, permanently discontinue and follow for PD • If at the end of the third week the creatinine level has improved to < Grade 1, resume study drug (maintain dose level) • If at the end of the third week the creatinine level has stabilized at Grade 1, resume study drug (decrease one dose level) • Following resumption of study drug, evaluate subject weekly x 2 weeks to ensure creatinine level does not worsen; if creatinine level again worsens during those 2 weeks, permanently discontinue and follow for PD
Grade 2	• Interrupt study drug • Evaluate subject weekly x 3 weeks • If during those 3 weeks, the creatinine level worsened at any time to > Grade 2, permanently discontinue and follow for PD

NCI CTCAE Toxicity Grade	Action
	• If at the end of the third week, the creatinine level has improved to < Grade 1 resume study drug (maintain dose level) • If at the end of the third week, the creatinine level has improved to a Grade 1 or has stabilized at Grade 2, resume study drug (decrease one dose level)

Table 6: Dose Reduction and Modification Guidelines (Continued)

NCI CTCAE Toxicity Grade	Action
	• Upon resumption of study drug, evaluate subject weekly x 2 weeks to ensure creatinine level does not worsen; if creatinine level again worsens during those 2 weeks, permanently discontinue and follow for PD
Grade 3	• Interrupt study drug • Evaluate subject weekly x 3 weeks • If during those 3 weeks, the creatinine level worsened at any time to > Grade 3, or if dialysis is indicated, permanently discontinue and follow for PD • If at the end of the third week, the creatinine level has improved to ≤ Grade 2 resume study drug (decrease one dose level) • Upon resumption of study drug, evaluate subject weekly x 2 weeks to ensure creatinine level does not worsen; if creatinine level again worsens during those 2 weeks, permanently discontinue and follow for PD • If at the end of the third week, the creatinine level has not improved to < Grade 3, permanently discontinue and follow for PD
Grade 4 OR if dialysis is indicated	• Permanently discontinue and follow for PD
Cairo-Bishop Toxicity Grade	
Clinical TLS ≥ Grade 2	• Interrupt lenalidomide therapy. • May resume lenalidomide when the TLS resolves to < Grade 1 (decrease one dose level)

Table 6: Dose Reduction and Modification Guidelines (Continued)

NCI CTCAE Toxicity Grade	**Action**	
Chemistry value	**Action**	**Lenalidomide Dose Modification**
• ALT > 3.0 and ≤ 5.0 x ULN AND • Serum total bilirubin ≤ 2.0 mg/dL (~1.5 x ULN)	• Continue current dose level • Test at next scheduled visit	• None Required – continue current dose level.
• ALT > 3.0 and ≤ 5.0 x ULN **AND** • Serum total bilirubin > 2.0 mg/dL (~1.5 x ULN)	• Temporarily Discontinue lenalidomide • Re-test weekly until ALT and total bilirubin return to baseline	• Resume the same dose of lenalidomide if recovery from the event is ≤ 14 days. • If recovery occurs > 14 days but ≤ 28 days, the lenalidomide dose should be decreased by one dose level, and weekly testing of liver functions should occur during that cycle. • If the event does not repeat, dose escalation or re-escalation may continue according to the protocol. • If the values do not return to baseline within 28 days, the medical monitor must be notified.
• ALT >5.0 x ULN **AND/OR** • Serum total bilirubin > 2.0 mg/dL (~1.5 x ULN)	• Temporarily Discontinue lenalidomide • Re-test weekly until ALT and total bilirubin return to baseline	• Resume the same dose of lenalidomide if recovery from the event is ≤ 14 days. • If recovery occurs > 14 days but ≤ 28 days, the lenalidomide dose should be decreased by one dose level, and weekly testing of liver functions should occur during that cycle. • If the event does not repeat, dose escalation or re-escalation may continue according to the protocol. • If the values do not return to baseline within 28 days, the medical monitor must be notified.

Table 6: Dose Reduction and Modification Guidelines (Continued)

NCI CTCAE Toxicity Grade	Action	
Other lenalidomide-related non-hematologic AEs	≥ Grade 3	• Interrupt lenalidomide therapy. • May resume lenalidomide when the adverse event resolves to ≤ Grade 2 (decrease one dose level or maintain dose level per the investigator's discretion)

A new course of treatment may begin on the scheduled Day 1 of a new cycle if:

- the ANC is ≥ 500/μL;
- the platelet count is ≥ 25,000/μL;
- any other lenalidomide-related non-hematologic adverse event that may have occurred has resolved as indicated in Table 6.

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly and a new cycle will not be initiated until the toxicity has resolved as described above.

Dose interruptions/reductions are permitted for Grade 1 or 2 adverse events at the investigator's discretion.

If a study drug interruption has lasted for 5 weeks, the investigator should contact the medical monitor to discuss whether the subject should be continued on the study.

Site staff are to contact Celgene to record new dose level and obtain new study drug assignment. If the treatment has been withheld and the next treatment cycle is delayed beyond 29 days after Day 1 of the prior treatment cycle, then Day 1 of the next treatment cycle will be defined as the first day that the treatment is resumed. If dose reduction occurs within a cycle, subjects will be given a new 28-day supply bottle, subjects should begin taking study drug at the current cycle day (ie, if reduction occurs on Cycle Day 16, then the subject will take study drug from the new bottle for the remainder of the cycle). Subjects will be required to return empty bottle or any unused drug prior to new drug being dispensed.

Dose re-escalation is permitted if the subject is able to complete 2 full cycles at the reduced dose level without experiencing a DLT or other toxicity deemed to be unacceptable by the investigator or subject. In the event the dose reduction is implemented due to Grade 4 neutropenia, subjects may be re-escalated after one full cycle at the lower dose level if the neutropenia resolves to a Grade 2 or better by the end of the cycle and no other DLT is observed. If that dose level is again not tolerated, the subject should be de-escalated to the dose below and remain at that tolerated dose level for the rest of the study.

Allopurinol Dose Adjustment Guidelines:

Allopurinol should be permanently discontinued for any adverse reaction deemed possibly related to allopurinol administration.

For a Grade 1 or 2 rash, allopurinol should be discontinued prior to study drug to try to determine causality. If the rash does not improve, the study drug should be adjusted per the investigator's discretion.

For a Grade 3 or 4 rash, allopurinol should be discontinued and study drug adjusted as outlined in Table 6.

In the event of development of renal impairment, allopurinol should be discontinued and study drug adjusted as outlined in Table 6.

For all other AEs, study drug should be adjusted as outlined above.

10.3. Blinding

This is now an open-label protocol. Therefore the dose of study drug will be identified on the package labeling (Amendment #10).

10.4. Emergency Unblinding

This is now an open-label protocol. Therefore the dose of study drug will be identified on the package labeling (Amendment #10).

[redacted]

10.6. Discontinuation from Treatment

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

- AEs that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of study drug.
- Disease progression with or without histologic transformation
- Subject withdraws consent

- Subject lost to follow-up
- Death
- Protocol violation

The reason for discontinuation should be recorded in the CRF and in the subject's medical records. Celgene is to be notified of all discontinuations from study drug.

11. EMERGENCY PROCEDURES

11.1. 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 and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on call Celgene/CRO 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.

12. STUDY DRUG MATERIALS AND MANAGEMENT

12.1. Supplier(s)

Celgene Corporation will supply lenalidomide capsules.

Celgene Corporation will no longer supply blinded allopurinol and matching placebo (Amendment #10).

Celgene Corporation will no longer supply lenalidomide (Amendment #11).

12.2. Dosage Form

Lenalidomide will be supplied as 2.5 mg, 5 mg, and 10 mg capsules for oral administration. Subjects dose reduced to 7.5 mg dose level (as outlined in Section 10.2.1) will receive one 5.0 mg capsule and one 2.5 mg capsule daily.

12.3. Dosage Regimen

Subjects will be randomized (1:1) via IVRS to receive the following:

- Oral lenalidomide 2.5 mg capsule once daily on days 1-28 of the first 28 day cycle and if tolerated should be escalated starting with the second cycle to a 5 mg capsule once daily on days 1-28 of a 28 day cycle up to disease progression.

  Following 5 continuous cycles at the 5 mg dose level, subjects who are tolerating the 5 mg dose level may be escalated to 10 mg once daily on days 1 through 28 of each 28-day cycle up to disease progression.

- Oral placebo capsule once daily every day for a 28 day cycle up to disease progression. The placebo treatment arm is discontinued in amendment #10.

Amendment #11:

Subjects currently on lenalidomide treatment will discontinue lenalidomide treatment immediately and complete the Treatment Discontinuation assessment. The subjects will then transition to the survival follow-up period.

12.4. Study Drug Packaging and Labeling

Celgene Corporation will supply lenalidomide 2.5 mg, 5 mg, and 10 mg capsules for oral administration. Subjects dose reduced to 7.5 mg dose level (as outlined in Section 10.2.1) will receive one 5.0 mg capsule and one 2.5 mg capsule daily.

The lenalidomide study drug will be packaged in 28-count bottles.

The label for study drug supplied by Celgene will bear Celgene's name and address, the protocol number, EudraCT number (where required), product name, dosage form, and strength, medication identification/kit number, dosing instructions, storage conditions, the quantity of study drug contained, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as needed and/or applicable

Subjects requiring dose reduction within a treatment cycle must return to the study site and return the empty bottles or any unused drug and a new bottle will be dispensed. Subjects will be given a new 28-day supply bottle and should begin taking study drug at the current cycle day.

12.5. Study Drug Receipt and Storage

The Investigator(s) is responsible for taking an inventory of each shipment of study drug received, and comparing it with the accompanying study drug shipping order form. The Investigator(s) will verify the accuracy of the information on the form and call Celgene to register the study medication received at the site.

At the study site, all investigational study drugs will be stored in a locked, safe area to prevent unauthorized access.

The study drug should be stored as directed on package label.

12.6. Record of Administration

Accurate recording of all study drug administration (including dispensing and dosing) will be made in the appropriate section of the subject's CRF and source documents.

12.7. Study Drug Accountability

The Investigator(s) or designee(s) is responsible for accounting for all study drug that is issued to and returned by the subject during the course of the study.

12.8. Study Drug Handling and Disposal

FCBP should not handle or administer study drug unless they are wearing gloves. All patients should not extensively handle or open study drug capsules and should maintain storage of capsules in the packaging until ingestion.

In investigational studies, study drug 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 patients. Once trained these healthcare staff will counsel patients prior to study drug being dispensed to ensure that the patient has complied with all requirements including use of birth control and pregnancy testing (FCBP) and that the patient understands the risks associated with lenalidomide. This step will be documented with a completed lenalidomide Education and Counseling Guidance Document (Appendix 22.6), and no drug will be dispensed until this step occurs. Counseling includes verification with the patient that required pregnancy testing was performed and results were negative. A Lenalidomide Information Sheet (Appendix 22.6) will be supplied with each study drug dispense.

Celgene will instruct the Investigator(s) on the return or destruction of unused study drug. If any study drug is lost or damaged, its disposition should be documented in the subject's CRF and source documents. Celgene will provide instructions for the return of study drug supplies at the end of the study.

13. ASSESSMENT OF EFFICACY

13.1. Assessments

- Survival/Date of death

13.2. Methods and Timing of Efficacy Assessments

Serial measurements of efficacy will be performed at baseline and at scheduled intervals throughout the duration of the study as outlined in Table 2. All scheduled visits will have a ± 3 day window unless otherwise stated.

14. ASSESSMENT OF SAFETY

14.1. Assessments

- Clinical laboratory evaluations:
  - Hematology: white blood cell (WBC), hemoglobin (HGB), hematocrit (HCT), platelet count, absolute neutrophil count (ANC), and absolute lymphocyte count (ALC)
  - Chemistry: calculated (method of Cockroft-Gault) creatinine clearance (screening only), potassium, calcium, phosphorus, creatinine, alkaline phosphatase, total bilirubin, AST/SGOT, ALT/SGPT, and uric acid
- Pregnancy testing for FCBP: serum or urine beta-human chorionic gonadotropin hormone (β-HCG) pregnancy testing with a sensitivity of at least 25 mIU/mL is to be done on FCBP only
  - FCBP should be monitored during the course of the study and after the end of study therapy to:
    - Ensure that pregnancy tests are performed during the course of the study and after end of study therapy and are negative (see specifics in Appendix 22.6).
    - Ensure the patient continues to practice abstinence or remains on adequate contraception (see specifics in Appendix 22.6).
    - If a FCBP becomes pregnant treatment should be stopped and the patient referred to the appropriate physician
- Male patients should be monitored during the course of the study and 28 days after the end of study therapy to:
  - Ensure they commit to continued abstinence from heterosexual contact or continue to use a condom during sexual contact with a FCBP
  - If a female partner of a male patient becomes pregnant she should be referred to an appropriate physician

[redacted]

- AEs by NCI CTCAE Version 3.0 with modifications recommended by the IWCLL guidelines for the diagnosis and treatment of chronic lymphocytic leukemia [redacted]
- Second primary malignancies will be monitored as events of interest and should be included as part of the assessment of adverse events throughout the course of the study. Investigators are to report any second primary malignancies as serious adverse events regardless of causal relationship to study drug, occurring at any time for the duration of the study, from the time of signing the informed consent up to and including the survival follow up phase.

14.2. Methods and Timing of Safety Assessments

Serial measurements of safety will be performed at baseline and at scheduled intervals throughout the duration of the study as outlined in Table 2. All scheduled visits will have a ± 3 day window unless otherwise stated. Abnormalities will be captured as adverse events. The adverse event of flare reaction, which may mimic disease progression, may render the efficacy assessments not evaluable at the corresponding visit(s). Cause of death is to be recorded in the CRF and the subject's medical record.

14.3. Recording and Reporting of Adverse Events

The recording and reporting of adverse events is described in Appendix 22.1.

16. STATISTICAL ANALYSES

16.1. Statistical Overview

The objective of the statistical analysis will be to compare the efficacy and safety of lenalidomide versus placebo as maintenance therapy in subjects with relapsed or refractory B-cell chronic lymphocytic leukemia (CLL) having achieved PR or better after second-line therapy.

Overall survival (OS) will be the primary endpoint for the protocol following amendment #10. This analysis will be performed at the completion of the study. It is estimated that at least 160 subjects across both treatment arms have died at the time of analysis (yielding 80% power to detect a 61.3% improvement in median OS for a two-sided test at 0.025 level allowing for one interim analysis).

16.2. Study Population Definitions

16.2.1. Intent-to-Treat Population

The primary efficacy analysis will be performed on the intent-to-treat (ITT) population, which will include all subjects who were randomized.

16.2.2. Safety Population

All randomized subjects who receive any study drug will be included in the safety analyses.

16.2.3. Subgroup Analyses

In addition to analyses that include all subjects, analyses will be performed to compare treatments within the following stratification subgroups:

- Response to second-line induction chemotherapy (PR, CRi or CR versus MRD-negative CR)
- Age (≤ 70 years versus > 70 years)
- Presence of at least one of the following poor prognostic factors: 11q deletion, 17p deletion, unmutated IgV_H or β2M > 4.0 mg/L (Yes versus No versus Unknown)

Additional subgroups may be examined, as needed based on regulatory and clinical requests.

16.3. Efficacy Evaluation

16.3.1. Primary Endpoint

Overall Survival (OS)

Overall survival is calculated as the time from randomization to death from any cause. OS will be censored at the last date that the subject was known to be alive for subjects who were alive at the time of analysis and for subjects who were lost to follow-up before death was documented.

The analysis of OS will include survival information for all randomized subjects. Subjects who discontinued from the treatment phase of the study and who had possibly received other anti-cancer therapies and then subsequently died will be included in the analysis as death. However, sensitivity analyses will be performed in which these subjects will be censored at the date of the first dose date of the anti-cancer therapy.

16.3.2. Secondary Endpoint

Progression Free Survival 2 (PFS2)

PFS is defines as the time from randomization to the second objective disease progression, or death from any cause, whichever occurs first. Patients alive and for whom a second objective disease progression has not been observed should be censored at the last time known to be alive and without second objective disease progression. In situations where OS and PFS2 cannot reliably be determined, it may be possible to rule out significant lack of efficacy of further treatments by looking at the outcome of the next line therapy. For this analysis, an event is defined as second objective disease progression, or death from any cause, or the start of the CLL therapy after next line treatment, whichever occurred first (EMEA guideline 13 DEC 2012). Various schemes will be assessed for missing data imputation if needed.

16.3.3. Efficacy Analyses

Kaplan-Meier product limit methods will be used to estimate the survivorship functions for the time-to-event endpoints (eg, OS, and PFS2). A two-sided log-rank test stratified by the 3 strata used in the randomization will be used as the primary analytic method to compare survivorship functions for time-to-event variables in the 2 treatment groups. In terms of the survivorship functions for each treatment group, the hypotheses of interest were:

H_0: $F_A(t) = F_P(t)$ for all t

Versus

H_1: $F_P(t) \neq F_A(t)$ for all t

where F_P is the survivorship function for placebo and F_A is the survivorship function for lenalidomide.

Median OS will be estimated using Kaplan-Meier estimates, and the 95% confidence intervals (CI) will be computed using the method of Brookmeyer and Crowley. Hazard ratio will be calculated using Cox model stratified for the 3 strata (ie, response to second-line induction chemotherapy, age, and presence of at least one prognostic factor) to account for the stratified randomization. The Cox model will also be used to identify prognostic factors.

Cross-tabulations will be provided by treatment group to summarize improvements from the best response during induction therapy.

16.4. Background and Demographic Characteristics

Subjects' age, weight, height, and other continuous demographic and baseline variables will be summarized using descriptive statistics (mean, standard deviation, minimum, and maximum), while performance status, gender, race, and other categorical variables will be summarized with frequency tabulations for each treatment group separately and pooled over both treatment

regimens. Medical history data will be summarized using frequency tabulations for each treatment arm separately and pooled over both arms. Individual subject listings will be provided.

Homogeneity of these variables will be assessed by one-way analysis of variance for continuous measures and Fisher's exact test for categorical measures.

16.5. Study Drug

Dosage statistics (mean, median, mode, standard deviation and final dose, dose at each evaluation) will be provided. Reasons for discontinuation will be summarized.

[redacted]

16.7. Safety Evaluation

All subjects who receive at least one dose of study medication will be included in the safety analyses.

Adverse events (AE) will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. The severity of the toxicities will be graded according to the NCI CTCAE version 3.0 whenever possible.

The adverse event of infection will also be analyzed according to the grading system as recommended by the IWCLL guidelines for the diagnosis and treatment of CLL [redacted] (Appendix 22.4).

AE frequency will be tabulated by body system, MedDRA preferred term for each treatment regimen during the Treatment Phase. In the by-subject analysis, a subject having the same event more than once will be counted only once. AEs will be summarized by worst NCI CTCAE version 3.0 grade. AEs leading to death or to discontinuation from treatment, events classified as NCI CTCAE version 3.0 Grade 3 or higher, study-drug-related events, serious adverse events (SAEs), and events of interest (including second primary malignancies) will be summarized separately.

Laboratory data will be graded according to NCI CTCAE version 3.0 severity grade. Cross tabulations will be provided to summarize frequencies of abnormalities.

For vital sign and body weight data, means, medians, standard deviations, minimum, and maximum values will be provided.

Graphical displays will be provided where useful to assist in the interpretation of results.

[redacted]

16.9. Sample Size and Power Considerations

For OS, a 61.3% improvement in median survival from randomization, from 3 years for placebo to 4.83 years on lenalidomide is considered clinically relevant. The OS is assumed to be exponential with a constant failure (hazard) rate. When the total number of events is approximately 160 over both treatment arms, then a two-sided log-rank test with an overall significance level of 0.025 (allowing for one interim analysis) would have 80% power to detect a hazard rate ratio of 0.62 (that is, if the survival curves are exponential, to detect a 61.3% difference in the median OS in the 2 arms). To ensure timely completion of the study, 320 subjects will be enrolled, 160 in each treatment arm. Enrollment will close once 320 subjects are randomized or 160 adjudicated PFS events are reached, whichever comes first.

17. QUALITY CONTROL AND QUALITY ASSURANCE

17.1. Monitoring

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. Before the study is initiated at a site visit or at an investigator meeting, all aspects of the study are reviewed with the investigator(s) and the staff. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, CRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs with the Investigator(s). Monitoring will include on-site visits with the Investigator(s) and his/her staff as well as any appropriate communications by mail, fax, or telephone. At each monitoring visit, the facilities, study drug storage area, CRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative for adherence to the protocol and Good Clinical Practice.

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

17.2. Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene. From time to time, representatives of this unit will conduct audits of clinical research activities in accordance with Celgene standard operating procedures (SOPs) to evaluate compliance with Good Clinical Practice guidelines and regulations.

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

17.3. Investigator(s) Responsibilities

Investigator responsibilities are set out in the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice and in the US Code of Federal Regulations. Celgene or a representative will contact and select all principal investigators or co-investigators who in turn will select their staff. The investigator must give the monitor access to relevant records to confirm the above.

The Investigator(s) is responsible for keeping a record of all subjects who sign an Informed Consent Form and are screened for entry into the study. For those subjects who fail screening, the reason(s) for exclusion must be recorded in the subject's source documents and in the IVRS system.

No procedure/assessment/measurement/test other than those outlined here, or in the schedule of study assessments, is to be performed without the prior written approval of Celgene, or unless deemed by the investigator(s) as necessary for the subject's medical care. Investigator(s) and/or authorized designee(s) must enter study data onto CRFs supplied by Celgene. The data on the CRF will be recorded in an anonymous manner to protect the subject's identity by using a unique identifier that will prevent personal identifiable information.

The Investigator(s), or a designated member of the Investigators' staff, must be available at some time during monitoring visits to review data and resolve any queries and to allow direct access to the subject's records (eg, medical records, office charts, hospital charts, and study related charts) for source data verification. The CRFs must be completed as soon as possible after the subject's visit but no later than prior to each monitoring visit and be made available to the Celgene representative(s) so that the accuracy and completeness may be checked.

18. REGULATORY CONSIDERATIONS

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

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki (Appendix 22.2). The review of this protocol by the IRB/IEC and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Patients and Part 56 Institutional Review Boards. Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC). A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to Celgene before the study initiation. The names and occupations of the chairman and the members of the IRB/IEC must be supplied to Celgene.

The Investigator(s) will be responsible for preparing documents for submission to the relevant IRB/IEC and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study.

A copy of the IRB/IEC approval for the protocol and the Informed Consent is to be provided to Celgene. The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number.

The Investigator(s) is responsible for notifying the IRB/IEC of any serious deviations from the protocol, or anything else that may involve added risk to subjects.

Any advertisements used to recruit subjects for the study must be reviewed and approved by Celgene and the IRB/IEC prior to use.

18.2. Protocol Amendments

Any amendment to this protocol that seems appropriate, as the study progresses (eg, affects safety or efficacy) will be agreed upon between the coordinating and/or principal investigator(s) and the Celgene study physician. Amendments will be submitted to the IRB/IEC for written approval before the implementation of the amended version. The written signed approval from the IRB/IEC should refer specifically to the investigator(s) and to the protocol number and title and mention any amendment numbers that are applicable. Celgene does not require that amendments that are administrative in nature receive IRB/IEC approval, but will be submitted to the IRB/IEC for information purposes. If local IRB/IEC procedures require approval of administrative amendments, then study sites should follow local IRB/IEC regulations.

18.3. Informed Consent

The Investigator(s) must obtain informed consent of a subject or his/her designee prior to any study related procedures as per Good Clinical Practices (GCP) as set forth in the 21 CFR Parts 50 and 56 and ICH guidelines.

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

18.4. Patient Confidentiality

Celgene affirms the patient's right to protection against invasion of privacy. In compliance with United States federal regulations, Celgene requires the Investigator(s) to permit Celgene's representatives and, when necessary, representatives of the FDA or other 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 patient's statement of informed consent, it is the responsibility of the Investigator(s) to obtain such permission in writing from the appropriate individual.

19. DATA HANDLING AND RECORDKEEPING

19.1. Data/Documents

The investigator(s) must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug, CRFs, source documents, original documents, data, records (eg, hospital records; clinical and office charts; laboratory notes; memoranda; patient's diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; patient files), and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study are complete, accurate, filed and retained.

19.2. Data Management

Data will be entered into the clinical database as per Celgene SOPs. These data will be electronically verified through use of on-line checks during data entry, and through 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, in the form of a Data Clarification Form (DCF). Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data. A quality control audit will be performed per Celgene SOP(s).

19.3. Retention of Records

The investigator(s) must maintain records of all study documents and supporting information relating to the conduct of the study. This documentation includes, but is not limited to, protocols, case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with health authorities and IRBs/IECs, informed consent forms, investigator(s) curricula vitae, monitoring visit logs, laboratory reference ranges, laboratory certification or quality control procedures, and laboratory director curriculum vitae. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice specified below. The study monitor must be consulted if the investigator(s) wishes to assign the study files to someone else, remove them to another location or is unable to retain them for a specified period.

For studies conducted in the United States under a US Investigational New Drug (IND), the investigator(s) must retain the study records for a minimum of 2 years after a marketing application for the indication is approved or for 2 years after the IND is withdrawn. If no application is filed, or if the application is not approved for the indication, the records are to be retained for two years after the investigation (ie, the IND) is discontinued, and FDA is notified of that fact. For IND studies conducted outside the US, the investigator(s), must retain study records for the time period described above or according to local laws or requirements, whichever is longer. The monitor will inform the investigator(s) of the dates for retention. All study documents should be made available if required by relevant health authorities. For studies not conducted under the US IND, the investigator(s) records must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no

pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by other applicable regulatory requirements.

20. PREMATURE DISCONTINUATION OF THE STUDY

20.1. Single Site

The responsible clinical Investigator as well as Celgene have the right to discontinue a single site at any time during the study for reasonable medical or administrative reasons. Possible reasons for termination of the study could be, but are not limited to:

- Unsatisfactory enrollment with respect to quantity or quality
- Inaccurate or incomplete data collection
- Falsification of records
- Failure to adhere to the study protocol

20.2. Study as a Whole

Celgene reserves the right to terminate this clinical study at any time for reasonable medical or administrative reasons.

Any possible premature discontinuation would have to be documented adequately with reasons being stated, and information would be issued according to local requirements (eg, IRB/IEC, regulatory authorities, etc.).

[redacted]

[redacted]

22. APPENDICES

22.1. Adverse Event

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence occurring at any dose 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 medical condition that was present prior to study treatment and that remains unchanged or improved should not be recorded as an AE. If there is a worsening of that medical condition, this should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the electronic Case Report Form rather than the individual signs or symptoms of the diagnosis or syndrome.

All AEs will be recorded by the Investigator(s) from the time of signing of informed consent form to 30 days after the treatment discontinuation visit. All AEs that lead to study discontinuation should be followed until resolution or stabilization. AEs will be recorded on the AE page of the CRF and in the subject's source documents.

Abnormal laboratory values defined as adverse events

An abnormal laboratory value is considered to be an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study.
- Requires treatment, modification/interruption of study drug dose, or any other therapeutic intervention.
- Is judged by the Investigator(s) to be of significant clinical importance.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE.

Please note that all ≥ Grade 3 hematologic lab abnormalities must be reported as an Adverse Event on the AE page of the CRF.

Serious adverse event

A serious adverse event (SAE) is any AE which:

- Results in death
- Is life-threatening (ie, in the opinion of the Investigator[s] the subject is at immediate risk of death from the AE)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- 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 serious adverse events. This includes any second primary malignancy, regardless of causal relationship to study medication, occurring at any time for the duration of the study, from the time of signing the ICF up to and including any follow-up, observation and/or survival follow-up period. In this study, subjects will be followed until all subjects in the study have been followed for at least 5 years from the last randomization, October 2020 (or have died/become lost to follow-up before 5 years). Events of second primary malignancy 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 of the diagnosis of the second primary malignancy must be provided at the time of reporting as a serious adverse event (eg, any confirmatory histology or cytology results).

Events not considered to be SAEs are hospitalizations which: were planned before entry into the clinical study; are for elective treatment of a condition unrelated to the studied indication or its treatment; occur on an emergency outpatient basis and do not result in admission (unless fulfilling other criteria above); are part of the normal treatment or monitoring of the studied indication and are not associated with any deterioration in condition.

If an AE is considered serious, both the AE pages of the CRF and the SAE Report Form must be completed.

For each SAE, the Investigator(s) will provide information on severity, start and stop dates, relationship to study drug, action taken regarding study drug, and outcome.

Classification of severity

For both AEs and SAEs, the investigator(s) must assess the severity of the event.

The severity of AEs will be graded based upon the subject's symptoms according to National Cancer Institute (NCI) Common Terminology Criteria (CTCAE, Version 3.0) with the exceptions recommended by the IWCLL guidelines for the diagnosis and treatment of chronic lymphocytic leukemia [redacted] AEs will be evaluated for severity according to the following scale:

Grade 1 = Mild

Grade 2 = Moderate

Grade 3 = Severe

Grade 4 = Life Threatening or disabling AE

Grade 5 = Death

The following exceptions will be made as recommended by the IWCLL guidelines for the diagnosis and treatment of chronic lymphocytic leukemia [redacted] as listed below*:

Grade#	Decrease in Platelets* or Hb° (nadir) From Pretreatment value (%)	Absolute neutrophil count/µL@ (nadir)
0	No change to 10%	≥ 2,000
1	11% - 24%	≥1,500 and < 2,000
2	25% - 49%	≥1,000 and < 1,500
3	50% - 74%	≥ 500 and < 1,000
4	≥ 75%	< 500

* Platelet counts must be below normal levels for grades 1-4. If, at any level of decrease the platelet count is < 20,000/µL, this will be considered grade 4 toxicity, unless a severe or life-threatening decrease in the initial platelet count (eg, 20,000/µL) was present pretreatment, in which case the patient is not evaluable for toxicity referable to platelet counts.

° Hb levels must be below normal levels for grades 1-4. Baseline and subsequent Hb determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity, but should be documented.

Grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, fatal. Death occurring as a result of toxicity at any level of decrease from pretreatment will be recorded as grade 5.

@ If the absolute neutrophil count (ANC) reaches less than 1,000/µL, it should be judged to be grade 3 toxicity. Other decreases in the white blood cell count, or in circulating granulocytes, are not to be considered, since a decrease in the white blood cell count is a desired therapeutic end point. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was less than 1,000/µL prior to therapy, the patient is not evaluable for toxicity referable to the ANC. The use of G-CSF is irrelevant for the grading toxicity, but should be documented.

Grade 4 hematologic abnormalities are expected in patients with CLL, and are also observed in patients receiving lenalidomide. During the conduct of CC-5013-CLL-002, all Grade 4 laboratory abnormalities will be reported to Celgene Drug Safety as SAEs at the discretion of the investigator and recorded in the CRF as SAEs, however those that are not deemed by the investigator to be part of a diagnosis or syndrome will not reported to the Health Authorities in an expedited manner. Laboratory values will be captured within the study database and will be reviewed on an ongoing basis by the sponsor and (provided that it is determined that any observed individual abnormalities or patterns of abnormalities do not warrant prompt communication to Health Authorities) will be reported to Health Authorities in periodic safety reports.

Please note that all ≥ Grade 3 hematologic lab abnormalities must be reported as an Adverse Event on the AE page of the CRF.

Classification of Relationship/Causality of adverse events (SAE/AE) to study drug

The Investigator(s) must determine the relationship between the administration of study drug and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected: The temporal relationship of the adverse event to study drug administration makes **a causal relationship unlikely or remote**, or other medications, therapeutic interventions, or

underlying conditions provide a sufficient explanation for the observed event

Suspected: The temporal relationship of the adverse event to study drug administration makes **a causal relationship possible,** and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

Monitoring and reporting of adverse events

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.

Immediate reporting of serious adverse events

Any AE that meets the criterion for a SAE requires the completion of a SAE Report Form in addition to being recorded on the AE pages of the CRF. The Investigator(s) is required to ensure that the data on these forms is accurate and consistent. This applies to all SAEs, regardless of relationship to study drug, that occur during the study, those made known to the Investigator(s) within 30 days after a subject's treatment discontinuation visit, and those made known to the investigator(s) at anytime that are suspected of being related to study drug.

Second primary malignancies will be monitored as events of interest and must be reported as serious adverse events. This includes any second primary malignancy, regardless of causal relationship to study medication, occurring at any time for the duration of the study, from the time of signing the ICF up to and including any follow-up, observation and/or survival follow-up period. In this study, subjects will be followed until all subjects in the study have been followed for at least 5 years from the last randomization, October 2020 (or have died/become lost to follow-up before 5 years). Events of second primary malignancy 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 of the diagnosis of the second primary malignancy must be provided at the time of reporting as a serious adverse event (eg, any confirmatory histology or cytology results).

Grade 4 hematologic abnormalities are expected in patients with CLL, and are also observed in patients receiving lenalidomide. The investigator will use their judgement to classify the seriousness of laboratory abnormality events. Laboratory values will be captured within the study database and will be reviewed on an ongoing basis by the sponsor and (provided that it is determined that any observed individual abnormalities or patterns of abnormalities do not warrant prompt communication to Heath Authorities) will be reported to Health Authorities in periodic safety reports.

The SAE must be reported (ie, within 24 hours of the Investigators' knowledge of the event) to the Celgene Safety by facsimile. An initial written report (prepared by the Investigator(s) using the SAE Report Form provided by Celgene) is to be faxed to the Safety Monitor (see below for contact information).

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

The Investigator(s) is responsible for informing the Institutional Review Board/Ethics Committee (IRB/IEC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator(s) must keep copies of all SAE information, including correspondence with Celgene and the IRB/IEC, on file. All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until either the event resolves completely, stabilizes/resolves with sequelae, or returns to baseline (if a baseline value is available).

Pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject or the female partner of a male subject occurring while the subject is on study drug, or within 28 days of the treatment discontinuation visit, are considered immediately reportable events. Study drug is to be discontinued immediately and the subject instructed to return any unused portion of the study drug to the investigator(s). The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Celgene Safety Monitor immediately by facsimile using the SAE Report Form.

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

The Investigator(s) will follow the female subject until completion of the pregnancy, and must notify Celgene Safety of the outcome of the pregnancy as a follow-up to the initial SAE report.

If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (ie, spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the Investigator(s) should follow the procedures for reporting SAEs (ie, report the event to Celgene Safety by facsimile within 24 hours of the Investigator's knowledge of the event).

In the case of a live "normal" birth, the Celgene Safety Monitor should be advised by telephone and facsimile within 24 hours of the Investigator's knowledge of the event.

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator(s) suspects is related to the in utero exposure to the study drug should also be reported to Celgene Safety by facsimile within 24 hours of the Investigators' knowledge of the event.

If the female is found not to be pregnant, any determination regarding the subject's continued participation in the study will be determined by the Investigator(s) and the Celgene Medical Monitor.

Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of reported events suspected of being related to lenalidomide based on the Investigator Brochure. Celgene Global Drug Safety will use the German Summary of Product Characteristics (SmPC) as the safety reference document for allopurinol.

For countries within the European Union, Celgene will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, AEs in accordance with the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

Celgene shall notify the Investigator of the following information:

- Any AE associated with the use of study drug in this study or in other studies that is both serious and unexpected, ie, suspected unexpected serious adverse reaction (SUSAR). Note that such cases from blinded studies will be unblinded for reporting purposes.
- Any finding from tests in laboratory animals that suggests a significant risk for human study subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

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

The Investigator must keep copies of all pertinent safety information, including correspondence with Celgene and the IRB/IEC, on file (see Section 19.3 for records retention information).

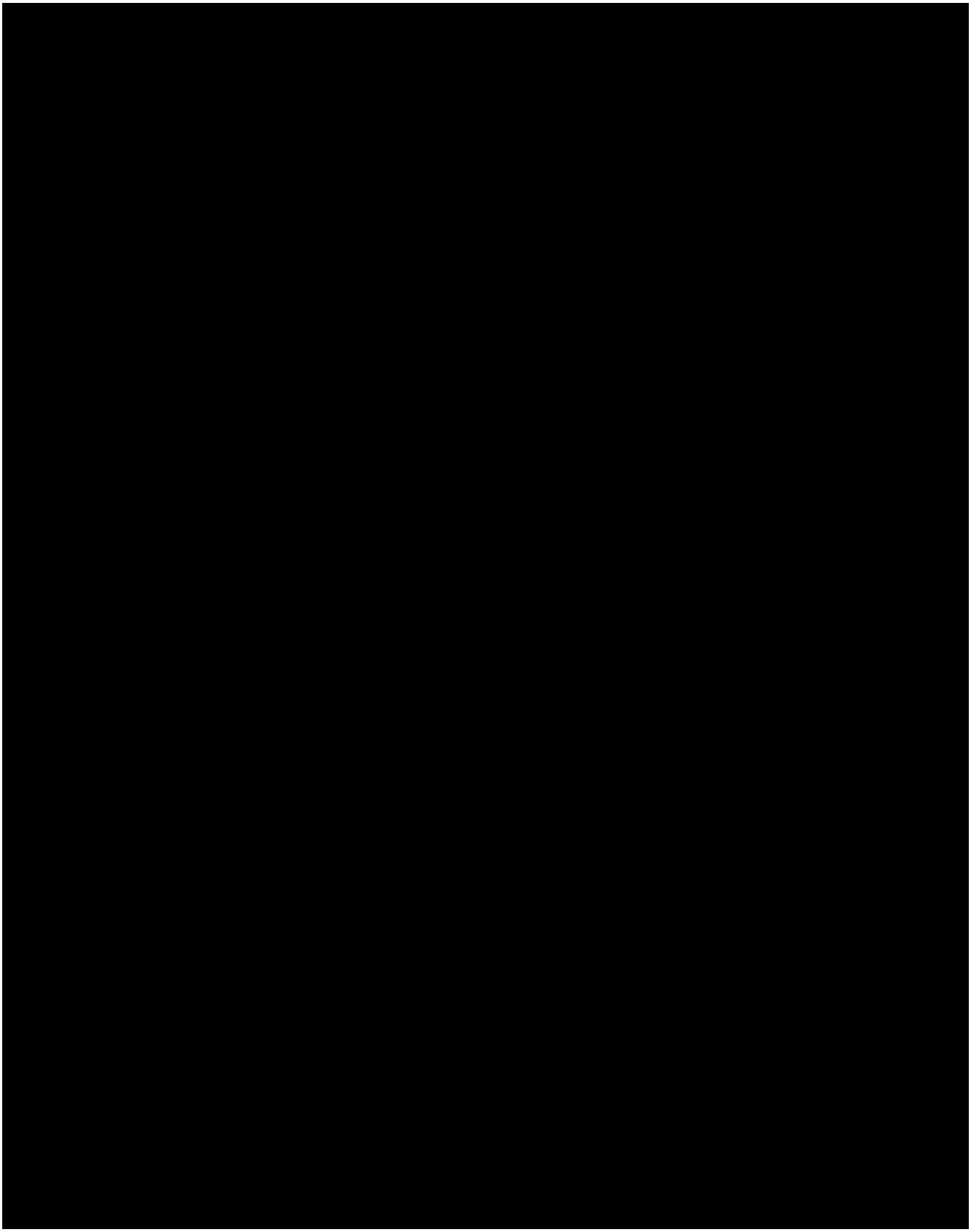
22.2. Declaration of Helsinki

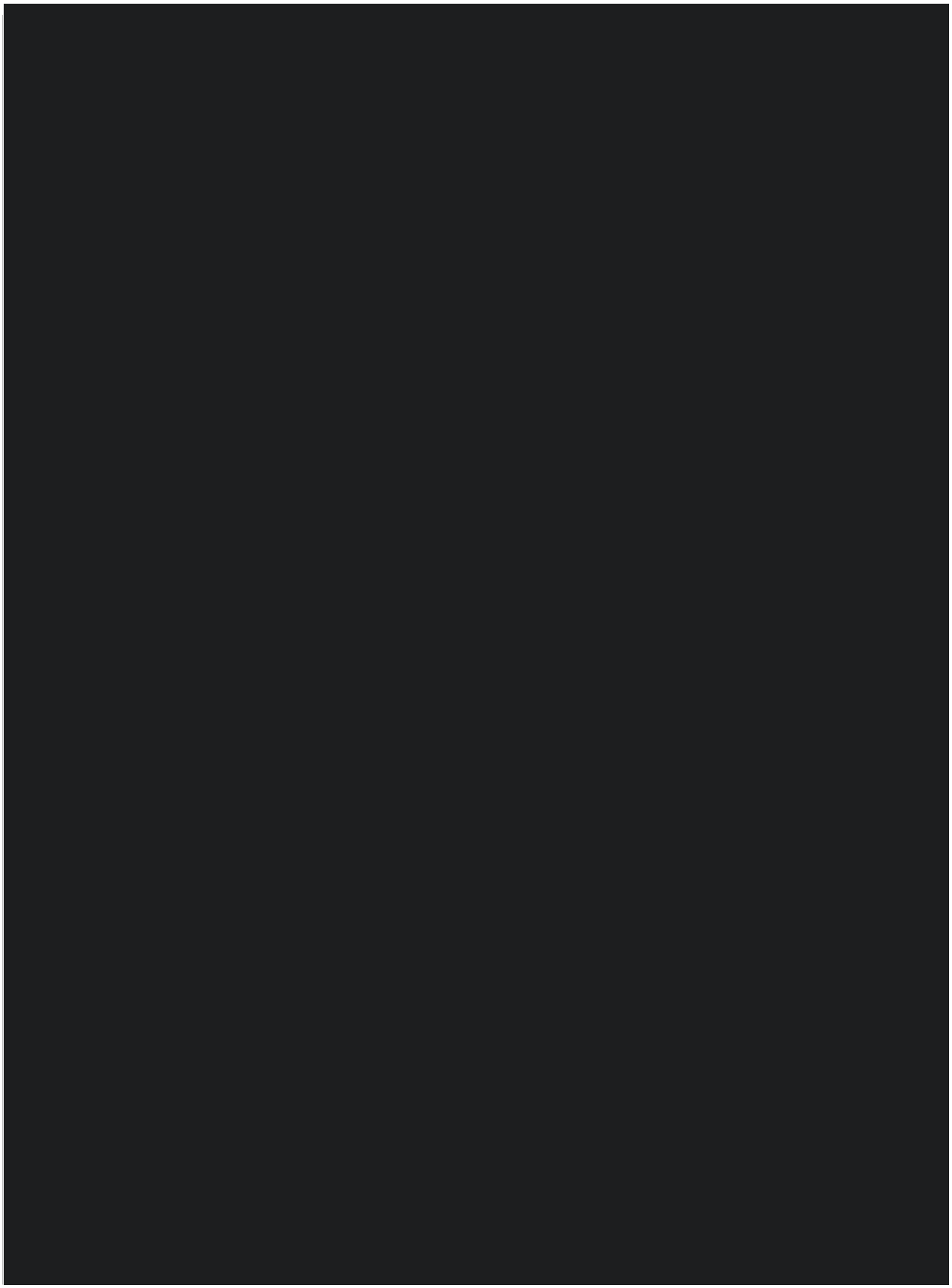
Celgene operates in accordance with the general ethical principles outlined in the Declaration of Helsinki.

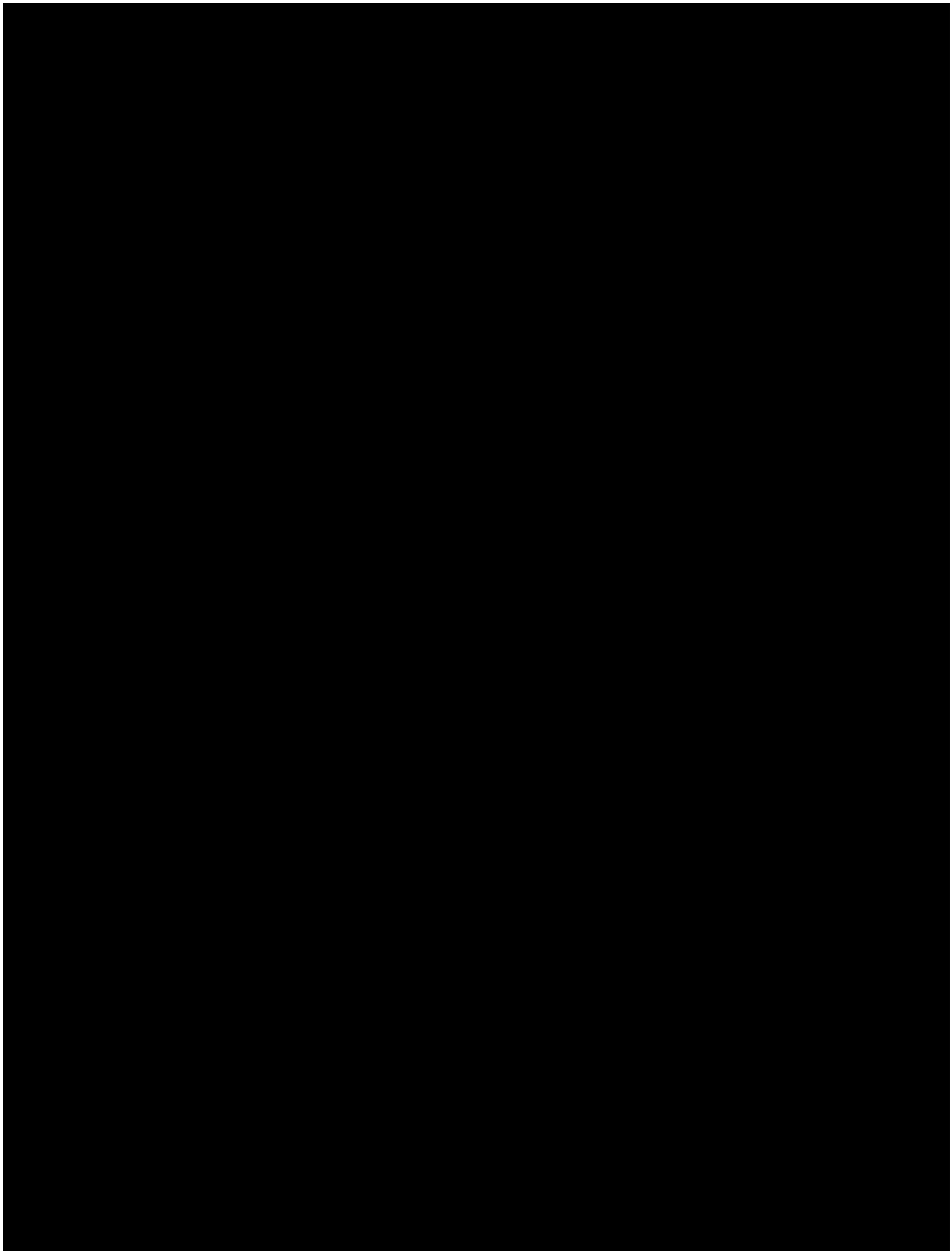
22.3. ECOG Performance Status Scale

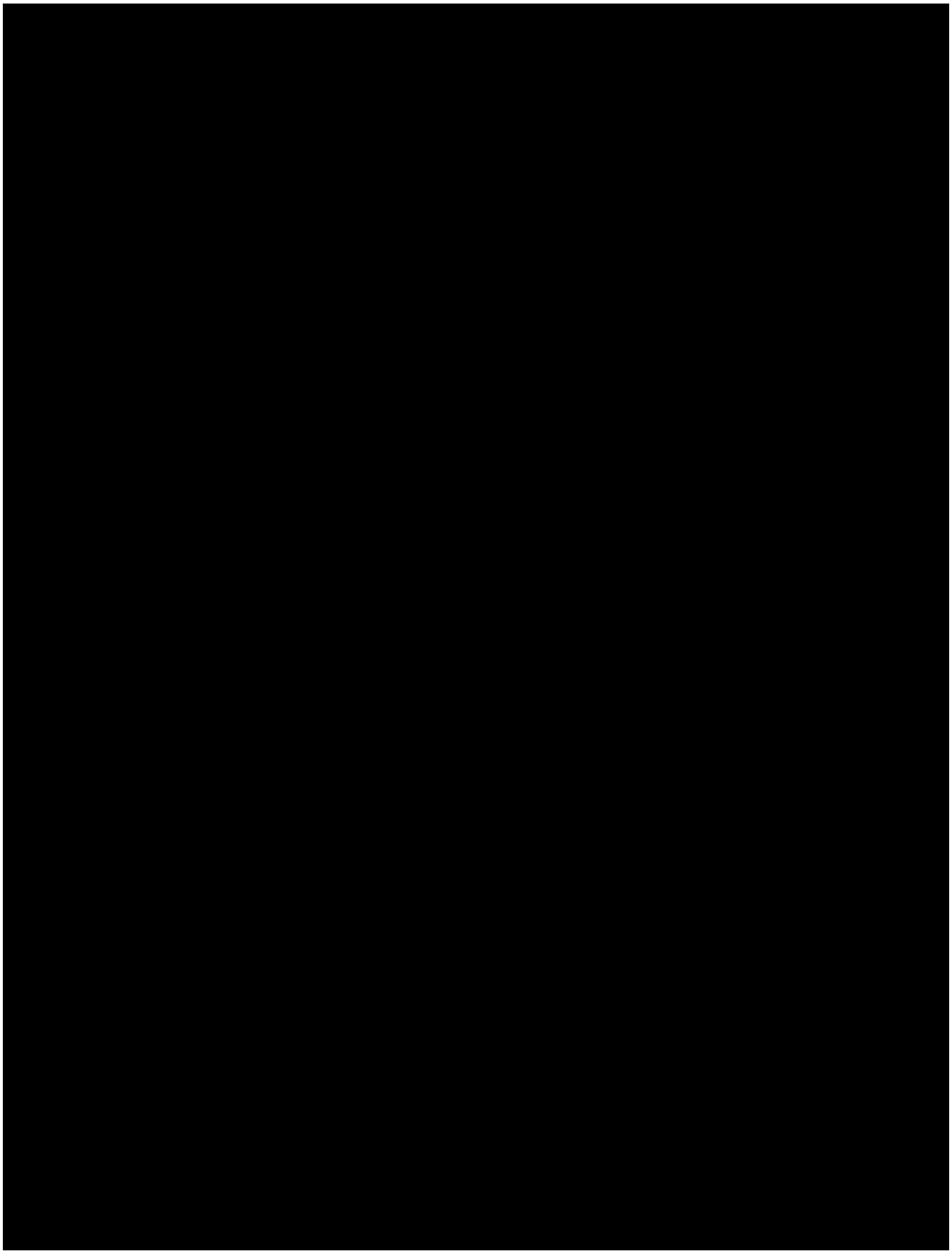
Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry our work of a light or sedentary nature, eg, light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

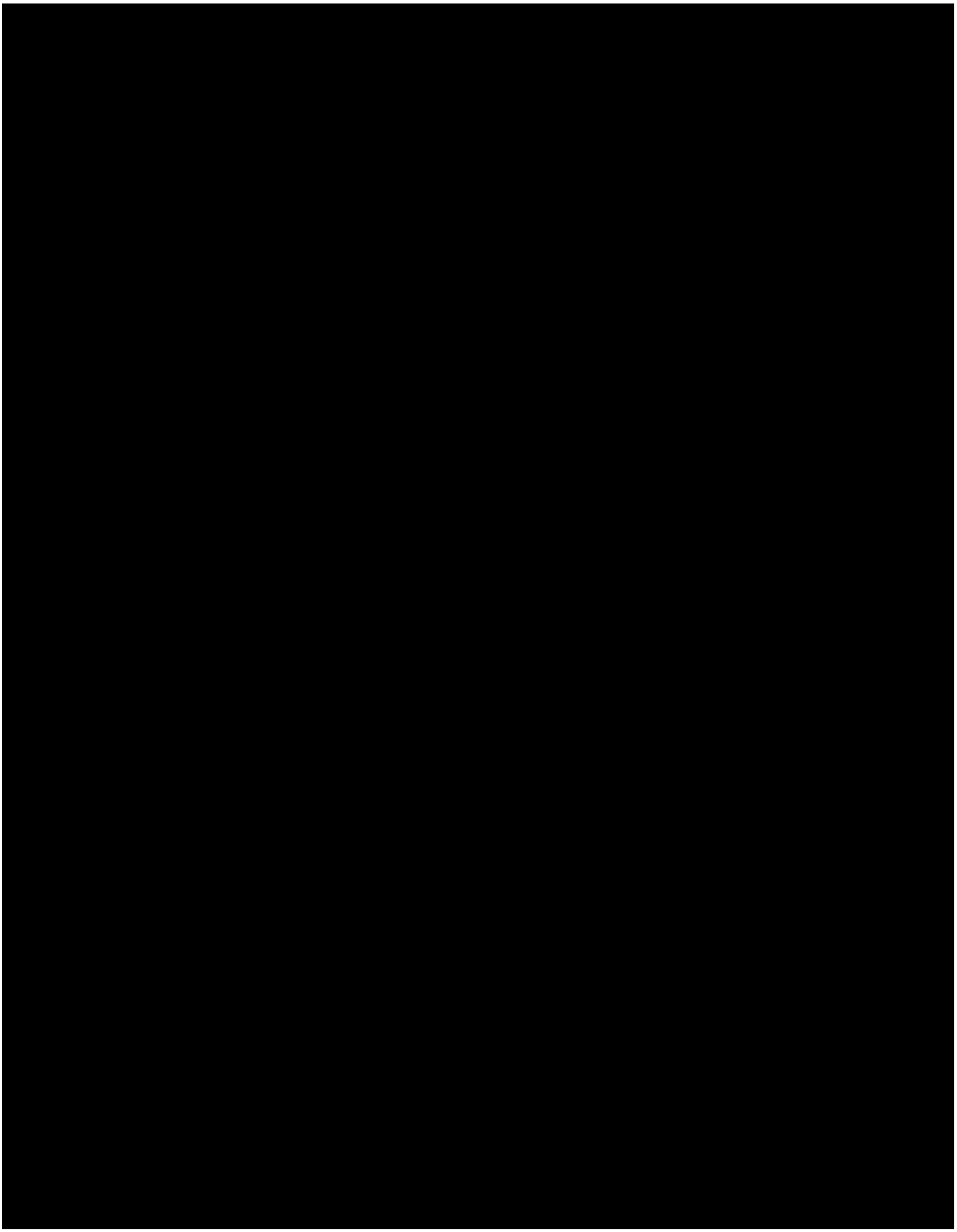
[redacted]

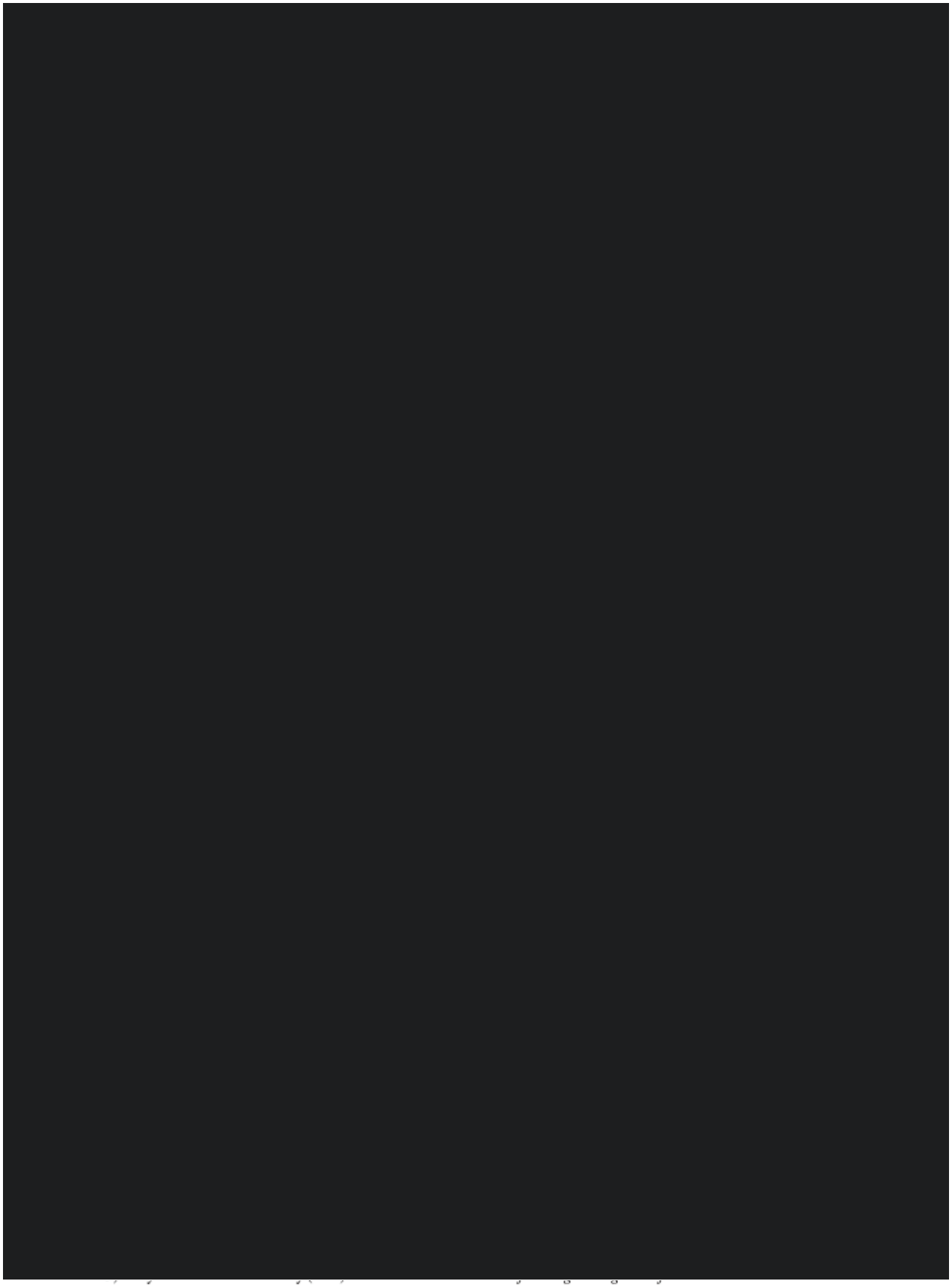


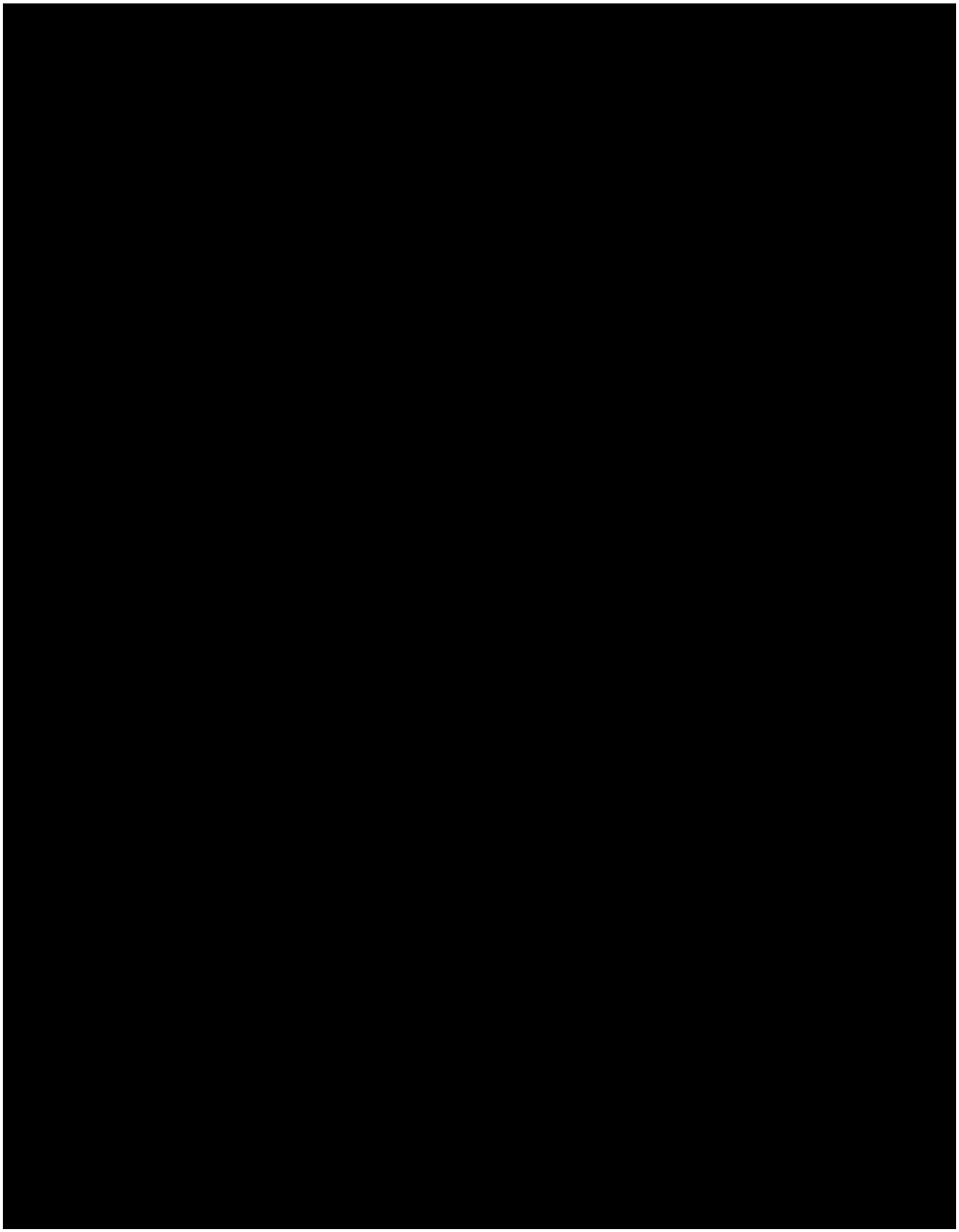


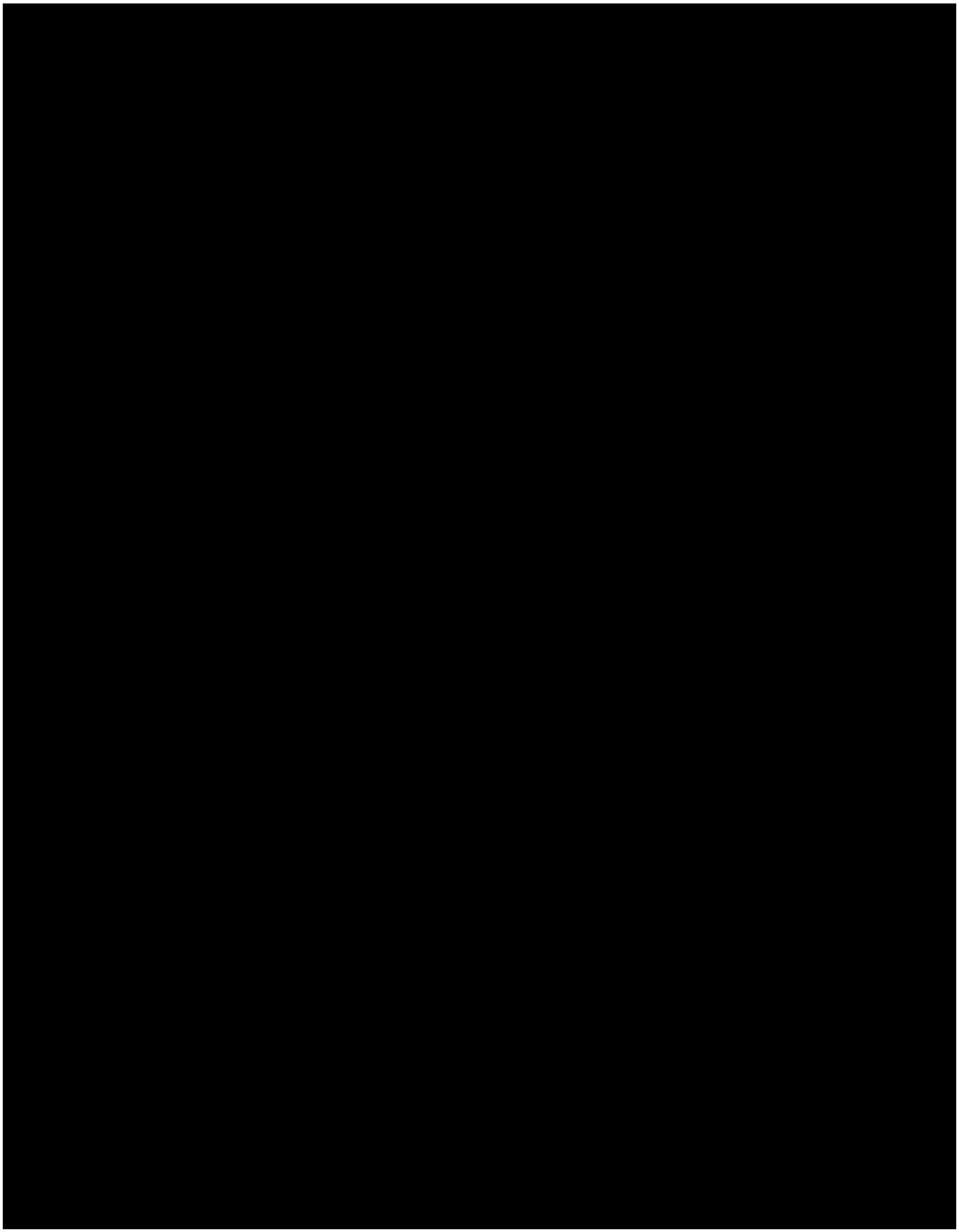


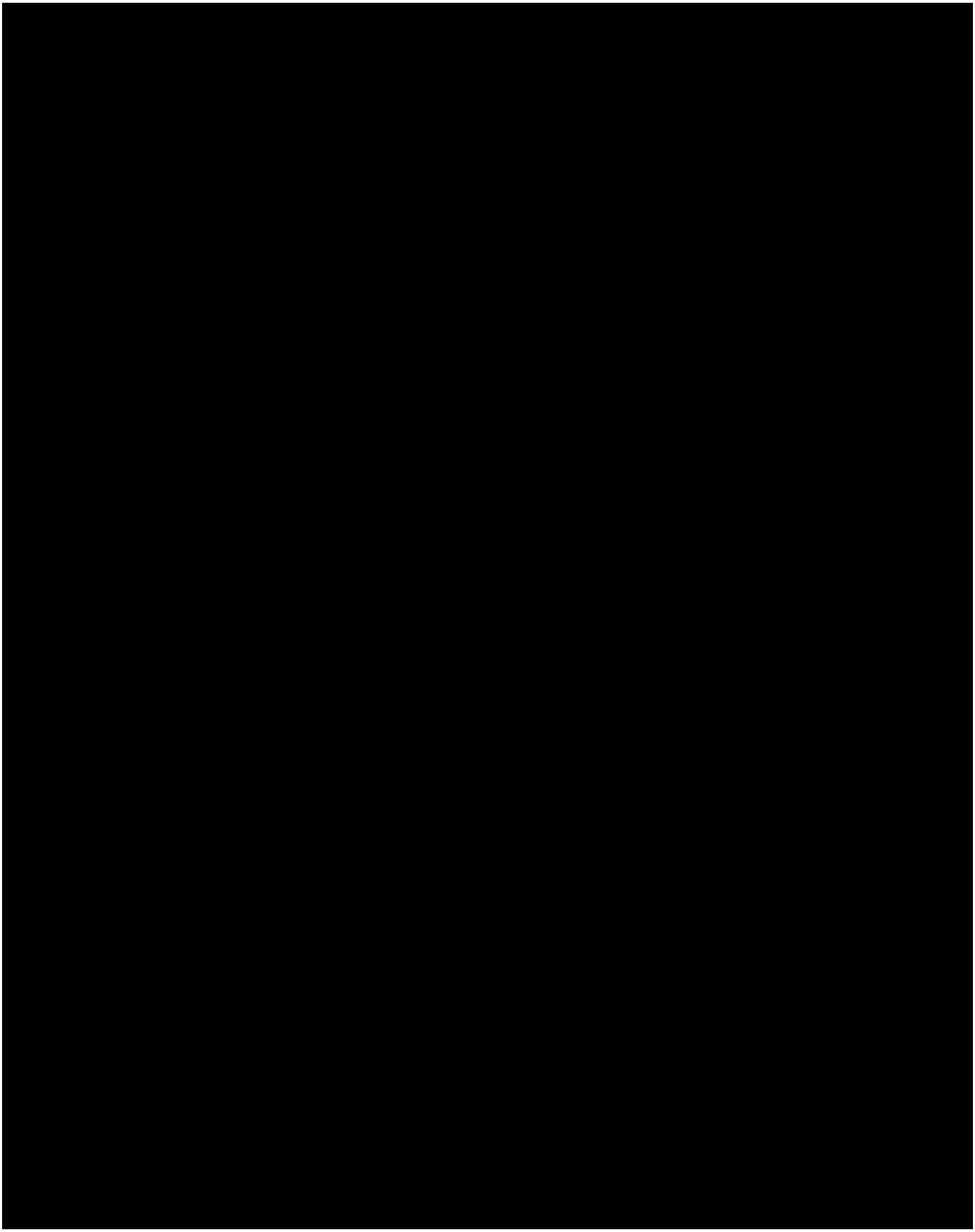


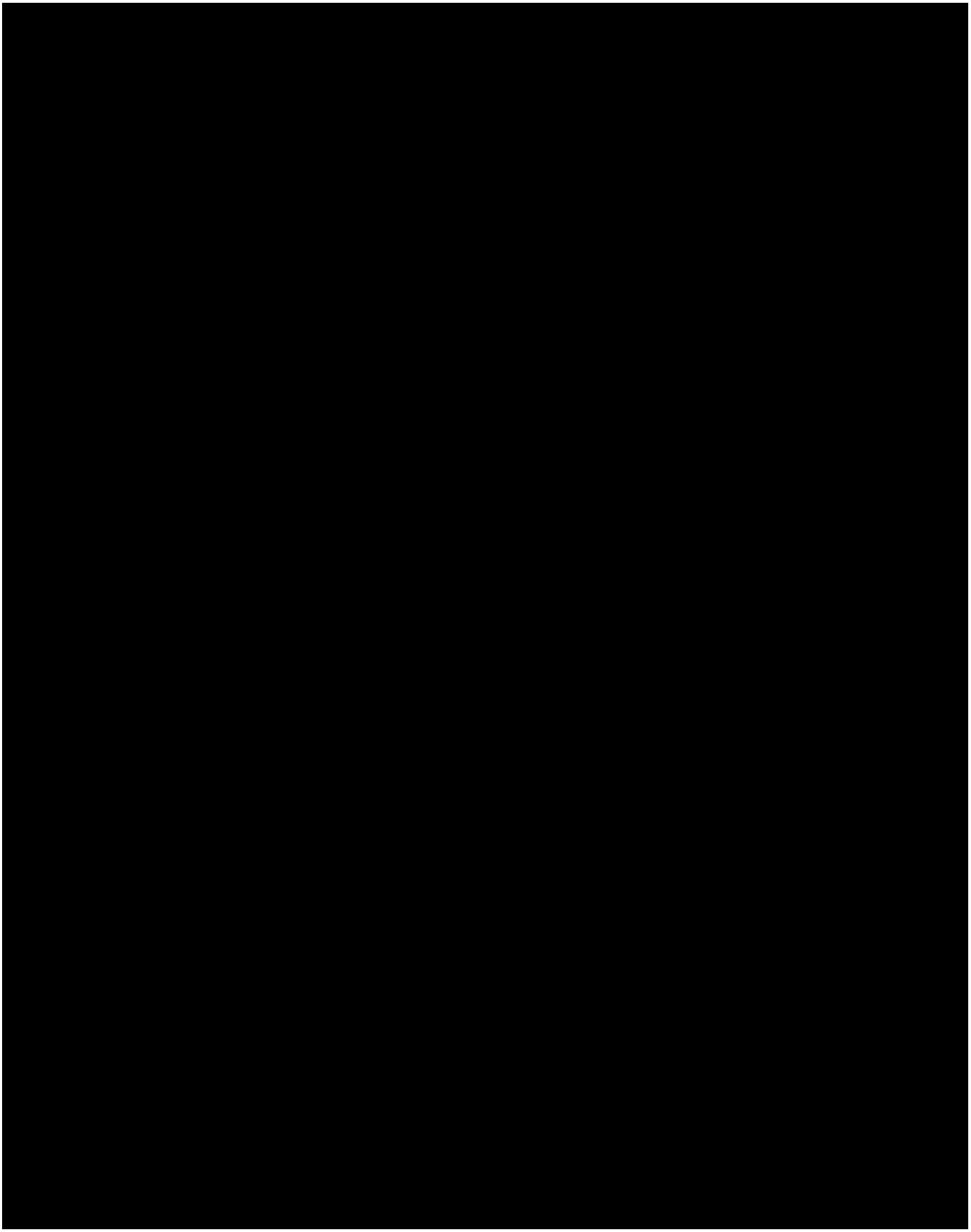












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22.6. Pregnancy Prevention Risk Management Plans

22.6.1. Lenalidomide Pregnancy Prevention Risk Management Plan

22.6.1.1. Lenalidomide Pregnancy Risk Minimisation Plan for Celgene Clinical Trials

Appendix 22.6.1 applies to all patients receiving lenalidomide therapy. The following Pregnancy Risk Minimisation Plan documents are included in this appendix:

1) Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods (Section 22.6.2);

2) Lenalidomide Education and Counseling Guidance Document (Section 22.6.2.1);

3) Lenalidomide Information Sheet (Section 22.6.2.2).

1. The Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods document (Section 22.6.2) provides the following information:
   - Potential risks to the fetus associated with lenalidomide exposure
   - Definition of Female of Childbearing Potential
   - Pregnancy testing requirements for patients receiving Lenalidomide who are females of childbearing potential
   - Acceptable birth control methods for both female of childbearing potential and male patients receiving Lenalidomide in the study
   - Requirements for counseling of all study patients receiving Lenalidomide about pregnancy precautions and the potential risks of fetal exposure to lenalidomide
2. The Lenalidomide Education and Counseling Guidance Document (Section 22.6.2.1) must be completed and signed by either a trained counselor or the Investigator at the participating clinical center prior to each dispensing of lenalidomide study treatment. A copy of this document must be maintained in the patient records.
3. The Lenalidomide Information Sheet (Section 22.6.2.2) will be given to each patient receiving lenalidomide study therapy. The patient must read this document prior to starting lenalidomide study treatment and each time they receive a new supply of study drug.

22.6.2. Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods

Risks Associated with Pregnancy

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

Criteria for females of childbearing potential (FCBP)

This protocol defines a female of childbearing potential as a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

Counseling

For a female of childbearing potential, lenalidomide is contraindicated unless all of the following are met (ie, all females of childbearing potential must be counseled concerning the following risks and requirements prior to the start of lenalidomide study therapy):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 4 weeks before starting study treatment, throughout the entire duration of study treatment, dose interruption and 28 days after the end of study treatment
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence the study treatment as soon as study drug is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing based on the frequency outlined in this protocol (Section 22.6.2)
- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide

The investigator must ensure that for females of childbearing potential:

- Complies with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding
- Acknowledge the aforementioned requirements

For a female NOT of childbearing potential, lenalidomide is contraindicated unless all of the following are met (ie, all females NOT of childbearing potential must be counseled concerning the following risks and requirements prior to the start of lenalidomide study therapy):

- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide

Traces of lenalidomide have been found in semen. Male patients taking lenalidomide must meet the following conditions (ie, all males must be counseled concerning the following risks and requirements prior to the start of lenalidomide study therapy):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a female of childbearing potential
- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a female of childbearing potential.

Contraception

Females of childbearing potential (FCBP) enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting study drug; 2) while participating in the study; 3) dose interruptions; and 4) for at least 28 days after study treatment discontinuation.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. FCBP must be referred to a qualified provider of contraceptive methods if needed. The following are examples of highly effective and additional effective methods of contraception:

- Highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants)
  - Tubal ligation
  - Partner's vasectomy
- Additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for females of childbearing potential, including females of childbearing potential who commit to complete abstinence, as outlined below.

Before starting study drug

Female Patients:

FCBP must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 10 to 14 days prior to the start of study drug and the second pregnancy test must be performed within 24 hours prior to the start of study drug. The patient may not receive study drug until the study doctor has verified that the results of these pregnancy tests are negative.

Male Patients:

Must practice complete 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 study drug discontinuation, even if he has undergone a successful vasectomy.

During study participation and for 28 days following study drug discontinuation

Female Patients:

- 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 study drug 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 study drug discontinuation.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days. If pregnancy or a positive pregnancy test does occur in a study patient, study drug must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a patient misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Study drug treatment must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after study drug discontinuation.

Male Patients:

- Counseling about the requirement for complete abstinence or condom use during sexual contact with a pregnant female or a female of childbearing potential and the

potential risks of fetal exposure to lenalidomide must be conducted at a minimum of every 28 days.

- If pregnancy or a positive pregnancy test does occur in the partner of a male study patient during study participation, the investigator must be notified immediately.

Additional precautions

- Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to the study doctor at the end of treatment.
- Female patients should not donate blood during therapy and for at least 28 days following discontinuation of study drug.
- Male patients should not donate blood, semen or sperm during therapy or for at least 28 days following discontinuation of study drug.
- Only enough study drug for one cycle of therapy may be dispensed with each cycle of therapy.

22.6.2.1. Lenalidomide Education and Counseling Guidance Document

To be completed prior to each dispensing of study drug.

Protocol Number: _____

Patient Name (Print): _____ DOB: _____/_____/_____ (mm/dd/yyyy)

(Check the appropriate box to indicate risk category)

Female: □

If female, check one:

- ❑ FCBP (Female of childbearing potential): sexually mature female who: 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time during the preceding 24 consecutive months)
- ❑ NOT FCBP

Male: □

Do Not Dispense study drug if:

- The patient is pregnant.
- No pregnancy tests were conducted for a FCBP.
- The patient states she did not use TWO reliable methods of birth control (unless practicing complete abstinence of heterosexual contact) [at least 28 days prior to therapy, during therapy and during dose interruption].

FCBP:

1. I verified that the required pregnancy tests performed are negative.
2. I counseled FCBP regarding the following:
   - Potential risk of fetal exposure to lenalidomide: If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking lenalidomide. The teratogenic potential of lenalidomide in humans cannot be ruled out. FCBP must agree not to become pregnant while taking lenalidomide.
   - Using TWO reliable methods of birth control at the same time or complete abstinence from heterosexual contact [at least 28 days prior to therapy, during therapy, during dose interruption and 28 days after discontinuation of study drug].
   - That even if she has amenorrhea she must comply with advice on contraception.

- Use of one highly effective method and one additional method of birth control AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:
  - Highly effective methods:
    - Intrauterine device (IUD)
    - Hormonal (birth control pills, injections, implants)
    - Tubal ligation
    - Partner's vasectomy
  - Additional effective methods:
    - Male condom
    - Diaphragm
    - Cervical Cap
- Pregnancy tests before and during treatment, even if the patient agrees not to have reproductive heterosexual contact. Two pregnancy tests will be performed prior to receiving study drug, one within 10 to 14 days and the second within 24 hours of the start of study drug.
- Frequency of pregnancy tests to be done:
  - Every week during the first 28 days of this study and a pregnancy test every 28 days during the patient's participation in this study if menstrual cycles are regular or every 14 days if cycles are irregular.
  - If the patient missed a period or has unusual menstrual bleeding.
  - When the patient is discontinued from the study and at day 28 after study drug discontinuation if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at days 14 and 28 after study drug discontinuation.
- Stop taking study drug immediately in the event of becoming pregnant and to call their study doctor as soon as possible.
- NEVER share study drug with anyone else.
- Do not donate blood while taking study drug and for 28 days after stopping study drug.
- Do not breastfeed a baby while participating in this study and for at least 28 days after study drug discontinuation.
- Do not break, chew, or open study drug capsules.
- Return unused study drug to the study doctor.

3. Provide Lenalidomide Information Sheet to the patient.

FEMALE NOT OF CHILDBEARING POTENTIAL (NATURAL MENOPAUSE FOR AT LEAST 24 CONSECUTIVE MONTHS, A HYSTERECTOMY, OR BILATERAL OOPHORECTOMY):

1. I counseled the female NOT of child bearing potential regarding the following:
   - Potential risks of fetal exposure to lenalidomide (Refer to item #2 in FCBP)
   - NEVER share study drug with anyone else.
   - Do not donate blood while taking study drug and for 28 days after stopping study drug.
   - Do not break, chew, or open study drug capsules.
   - Return unused study drug capsules to the study doctor.
2. Provide Lenalidomide Information Sheet to the patient.

MALE:

1. I counseled the Male patient regarding the following:
   - Potential risks of fetal exposure to lenalidomide (Refer to item #2 in FCBP).
   - To engage in complete abstinence or use a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or a female of childbearing potential, while taking study drug, during dose interruptions and for 28 days after stopping study drug.
   - Males should notify their study doctor when their female partner becomes pregnant and female partners of males taking study drug should be advised to call their healthcare provider immediately if they get pregnant.
   - NEVER share study drug with anyone else.
   - Do not donate blood, semen or sperm while taking study drug and for 28 days after stopping study drug.
   - Do not break, chew, or open study drug capsules.
   - Return unused study drug capsules to the study doctor.
2. Provide Lenalidomide Information Sheet to the patient.

Investigator/Counselor Name (Print): _____

(circle applicable)

Investigator/Counselor Signature: _____ Date: _____/_____/_____

(circle applicable)

Maintain a copy of the Education and Counseling Guidance Document in the patient records.

22.6.2.2. Lenalidomide Information Sheet

FOR PATIENTS ENROLLED IN CLINICAL RESEARCH STUDIES

Please read this Lenalidomide Information Sheet before you start taking study drug and each time you get a new supply. This Lenalidomide Information Sheet does not take the place of an informed consent to participate in clinical research or talking to your study doctor or healthcare provider about your medical condition or your treatment.

What is the most important information I should know about lenalidomide?

1. **Lenalidomide may cause birth defects (deformed babies) or death of an unborn baby.** Lenalidomide is similar to the medicine thalidomide. It is known that thalidomide causes life-threatening birth defects. Lenalidomide has not been tested in pregnant women but may also cause birth defects. Findings from a monkey study indicate that lenalidomide caused birth defects in the offspring of female monkeys who received the drug during pregnancy.

   If you are a female who is able to become pregnant:

   - **Do not take study drug if you are pregnant or plan to become pregnant**
   - **You must practice complete abstinence or use two reliable, separate forms of effective birth control at the same time:**
     - for 28 days before starting study drug
     - while taking study drug
     - during dose interruptions of study drug
     - for 28 days after stopping study drug
   - **You must have pregnancy testing done at the following times:**
     - within 10 to 14 days and again 24 hours prior to the first dose of study drug
     - weekly for the first 28 days
     - every 28 days after the first month or every 14 days if you have irregular menstrual periods
     - if you miss your period or have unusual menstrual bleeding
     - 28 days after the last dose of study drug (14 and 28 days after the last dose if menstrual periods are irregular)
   - **Stop taking study drug if you become pregnant during treatment**
     - If you suspect you are pregnant at any time during the study, you must stop study drug immediately and immediately inform your study doctor. Your study doctor will report all cases of pregnancy to Celgene Corporation
   - **Do not breastfeed while taking study drug**

- The study doctor will be able to advise you where to get additional advice on contraception.

If you are a female not of childbearing potential:

In order to ensure that an unborn baby is not exposed to lenalidomide, your study doctor will confirm that you are not able to become pregnant.

If you are a male:

Lenalidomide is detected in trace quantities in human semen. The risk to the foetus in females of childbearing potential whose male partner is receiving lenalidomide is unknown at this time.

- Male patients (including those who have had a vasectomy) must practice complete abstinence or must use a condom during sexual contact with a pregnant female or a female that can become pregnant:
  - While you are taking study drug
  - During dose interruptions of study drug
  - For 28 days after you stop taking study drug
- **Male patients should not donate sperm or semen** while taking study drug and for 28 days after stopping study drug.
- **If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation. Your partner should call their healthcare provider immediately if they get pregnant.**

2. **Restrictions in sharing study drug and donating blood:**
   - **Do not share study drug with other people. It must be kept out of the reach of children and should never be given to any other person.**
   - **Do not donate blood** while you take study drug and for 28 days after stopping study drug.
   - **Do not break, chew, or open study drug capsules.**
   - You will get no more than a 28-day supply of study drug at one time.
   - Return unused study drug capsules to your study doctor.

Additional information is provided in the informed consent form and you can ask your study doctor for more information.

– SUMMARY OF CHANGES –

AMENDMENT NO. 11

A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY OF THE EFFICACY AND SAFETY OF LENALIDOMIDE (REVLIMID®) AS MAINTENANCE THERAPY FOR PATIENTS WITH B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA FOLLOWING SECOND-LINE THERAPY

(THE CONTINUUM TRIAL)

INVESTIGATIONAL PRODUCT (IP):	Lenalidomide
PROTOCOL NUMBER:	CC-5013-CLL-002
ORIGINAL DATE:	15 Jan 2008
AMENDMENT No. 11 DATE:	16 March 2018
EudraCT NUMBER:	2007-0016-26-27
IND NUMBER:	060100

[redacted]

CONFIDENTIAL

This protocol is provided to you as an Investigator, potential Investigator, or consultant for review by you, your staff, and ethics committee/institutional review board. The information contained in this document is regarded as confidential and, except to the extent necessary to obtain informed consent, may not be disclosed to another party unless such disclosure is required by law or

regulations. Persons to whom the information is disclosed must be informed that the information is confidential and may not be further disclosed by them.

[redacted]

[redacted]

[redacted]

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[redacted]

[redacted]

A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY OF THE EFFICACY AND SAFETY OF LENALIDOMIDE (REVLIMID®) AS MAINTENANCE THERAPY FOR PATIENTS WITH B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA FOLLOWING SECOND-LINE THERAPY

(THE CONTINUUM TRIAL)

STUDY DRUG:	Lenalidomide
PROTOCOL NUMBER:	CC-5013-CLL-002
EUDRACT NUMBER:	2007-001626-27
DATE FINAL:	15 January 2008
AMENDMENT [redacted] #11:	[redacted] 16 March 2018

[redacted]

CONFIDENTIAL

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COORDINATING PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Original Protocol: 15 January 2008

Amendment #1: 12 August 2008

Amendment #2: 23 September 2008

Amendment #3: 17 October 2008

Amendment #4: 6 May 2009

Amendment #5: 28 June 2010

Amendment #6: 4 May 2011

Amendment #7: 7 October 2011

Amendment #8: 4 October 2012

Amendment #9: 24 April 2015

Amendment #10: 13 May 2016

Amendment #11: 16 March 2018

Signature of Coordinating Principal Investigator **dd/mmm/yy**

Printed Name of Coordinating Principal Investigator and Title

Site Number_____

By my signature, I agree to supervise and oversee the conduct of this study and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board/Independent Ethics Committee (IRB/IEC) procedures, instructions from Celgene representatives, the Declaration of Helsinki, International Conference on Harmonisation (ICH) Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations and local regulations governing the conduct of clinical studies.

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Original Protocol: 15 January 2008

Amendment #1: 12 August 2008

Amendment #2: 23 September 2008

Amendment #3: 17 October 2008

Amendment #4: 6 May 2009

Amendment #5: 28 June 2010

Amendment #6: 4 May 2011

Amendment #7: 7 October 2011

Amendment #8: 4 October 2012

Amendment #9: 24 April 2015

Amendment #10: 13 May 2016

Amendment #11: 16 March 2018

Signature of Site Principal Investigator **dd/mmm/yy**

Printed Name of Site Principal Investigator and Title

Site Number_____

By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, IRB/IEC procedures, instructions from Celgene representatives, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations and local regulations governing the conduct of clinical studies.

[redacted]

3. SYNOPSIS

Name of Sponsor/Company: Celgene Corporation
Name of Investigational Product: lenalidomide
Protocol Number: CC-5013-CLL-002
Protocol Title: A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY OF THE EFFICACY AND SAFETY OF LENALIDOMIDE (REVLIMID®) AS MAINTENANCE THERAPY FOR PATIENTS WITH B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA FOLLOWING SECOND-LINE THERAPY
Indication: Maintenance therapy in subjects with relapsed or refractory B-cell chronic lymphocytic leukemia (CLL) who have achieved at least partial response (PR) to second-line therapy.

Study Duration: Subjects randomized to the lenalidomide treatment arm and on treatment at the time of Amendment #10 may, at the discretion of the investigator, continue on lenalidomide study treatment until disease progression (PD) develops ~~or until October 2020, whichever comes first~~. Subjects randomized to the placebo treatment arm and on treatment at the time of Amendment #10 will enter the survival follow-up period. Subjects who discontinue study treatment prematurely for reasons other than PD and subjects who develop PD (including disease transformation) will enter the survival follow-up period.

Subjects will be followed until all subjects in the study have been followed for at least 5 years from the last randomization, October 2020, (or have died/become lost to follow-up before the 5 years).

Amendment #11:

[redacted] ~~s~~Subjects currently on lenalidomide [redacted] treatment will [redacted] ~~-d~~discontinue lenalidomide [redacted] ~~t~~treatment immediately and [redacted] ~~s~~complete the Treatment Discontinuation assessment. The subjects will then transition to the survival follow-up period.

Phase of development:
Phase 3

Objectives:

Primary:

- To compare the efficacy of lenalidomide *versus* placebo maintenance therapy.

Secondary:

- To evaluate the safety of lenalidomide *versus* placebo maintenance therapy.

Study Endpoints:

Primary

- Overall Survival (OS)

Secondary

- Safety [type, frequency, and severity of adverse events (AEs) and relationship of AEs to lenalidomide]
- Progression-free survival 2 (PFS2)

[redacted]

Study Design:

CC-5013-CLL-002 is a phase 3, multicenter, randomized, placebo-controlled, parallel-group study that will compare the efficacy and safety of oral lenalidomide maintenance therapy to that of placebo in patients with B-cell CLL who achieved at least partial response (PR) with second-line therapy. The primary efficacy objective of this study is to demonstrate superiority of lenalidomide over placebo in prolonging overall survival (OS) due to continued therapy, for all subjects, including subjects with or without poor prognostic factors, subjects of various ages and subjects with PR, nodular partial response (nPR), complete response with incomplete bone marrow recovery (CRi), complete response (CR) and minimal residual disease (MRD)-negative CR. All subjects randomized to the lenalidomide treatment arm, including those subjects who do not improve their response (PR, nPR, CRi or CR) and subjects who do not have the opportunity to improve their response further (MRD-negative CR) will be treated up to disease progression [redacted], with the objective to demonstrate prolongation of OS.

Eligible subjects must have been treated with a purine analog-, a bendamustine-, an anti-CD20-antibody-, or a chlorambucil-based regimen in first and/or second line and must have achieved at least PR to second-line induction therapy of sufficient duration. Alemtuzumab- containing regimens will also be allowed for those subjects with 17p deletion. Subjects who achieve stable disease (SD) only or who develop progressive disease (PD) at any time during induction therapy will not be eligible for participation in this study.

Approximately, three hundred twenty (320) subjects with PR, nPR, CRi, CR or MRD-negative CR will be enrolled and randomized (1:1) into two arms: placebo daily or lenalidomide 2.5 mg daily on days 1-28 of the first 28-day cycle. If the 2.5 mg dose level is well tolerated, escalation to 5 mg daily on days 1-28 of each 28-day cycle is permitted starting with the second cycle; for those subjects who tolerate well the 5 mg dose, escalation to 10 mg daily on days 1-28 of each 28-day cycle after 5 continuous cycles at 5 mg will be permitted.

Each treatment arm will be stratified according to 1) the response to second-line induction therapy (PR, nPR, CRi or CR versus MRD-negative CR); 2) age ($\leq$ 70 versus > 70 years); and 3) presence of at least one of the following poor prognostic factors: 11q deletion, 17p deletion, unmutated IgVH or β2M > 4.0 mg/L (Yes versus No versus Unknown).

The subjects randomized to the lenalidomide treatment arm will continue to receive lenalidomide study drug up to PD [redacted]. Subjects who discontinue therapy, will enter the survival follow-up phase of the study. Subjects will be assessed for subsequent CLL therapies, second primary malignancies, recovery from serious

adverse events (SAEs), and any new SAEs or AEs related to study procedures or prior maintenance therapy.

Subjects randomized to the placebo arm and currently on treatment at the time of Amendment #10 and patients who previously discontinued from the study drug and will be followed every 24 weeks for survival, subsequent CLL therapies, response to next therapy and progression following next therapy, and second primary malignancies. Subjects will be followed until all subjects in the study have been followed for at least 5 years from the last randomization, October 2020 (or have died/become lost to follow-up before 5 years).

Amendment #11:

Subjects currently on lenalidomide treatment will discontinue lenalidomide treatment immediately and complete the Treatment Discontinuation assessment. The subjects will then transition to the survival follow-up period.

Screening

Subjects will sign informed consent prior to undergoing any study-related procedures. Screening assessments for protocol eligibility will be performed within 28 days prior to randomization as outlined in Table 2: Schedule of Assessments. Subjects who develop PD during screening will not be eligible to enroll into this study.

All subjects will undergo both bone marrow aspirate and bone marrow biopsy procedures during screening. MRD status will be assessed by peripheral blood and bone marrow flow cytometry at entry into the study for those subjects who achieved a complete response (CR) to second-line induction therapy. Peripheral blood flow cytometry will be performed for all subjects at entry to confirm disease diagnosis by immunophenotyping and to perform immune cell (NK and T cell) analyses. If subjects enter the study with MRD negativity, the disease diagnosis will be confirmed based on prior flow cytometry (documentation needed). MRD status, immunophenotyping, and immune cell analyses will be performed at a central laboratory.

A peripheral blood sample for direct antiglobulin test (DAT) will be collected during screening and analyzed at a central laboratory.

Before randomization, subjects will be tested for cytogenetics by FISH, IgV_H mutational status, and β2M. The β2M test will be performed during screening using a peripheral blood sample and analyzed at a central laboratory.

FISH and IgV_H testing will be performed prior to second line, during second line, in the interval between second-line therapy, and screening or during the screening period using a peripheral blood sample. Because test results cannot be obtained during screening or between second line and screening in some subjects who achieve a good response due to the limited number of remaining CLL cells, we recommend conducting the FISH and IgV_H tests preferably prior to second line or during second line.

Samples for FISH and IgV_H will be analyzed at a central laboratory.

If tests do not yield results, subjects can be randomized and stratified based on historical data.

Those subjects for whom results were not obtainable pre-randomization and for whom no historical data were available will be enrolled and grouped separately.

During screening, CT scans of the chest, abdomen and pelvis will also be performed for all subjects; in particular, they will be used to document the status (PR or CR) of subjects entering the study.

If, during the screening period, the subject has a correctable event that prevents randomization and the event cannot be corrected within the 28 day screening period, the subject may be re-

screened; however, the CT scans and bone marrow aspirate and biopsy will not need to be repeated if those tests were implemented within 56 days prior to randomization and the subject's clinical status remains the same.

Randomization

Randomization must occur no less than 8 weeks (56 days) and no greater than 20 weeks (140 days) from the last day of the last cycle of second-line induction therapy received by the subject in order for the subject to be eligible for enrollment into this study. Subjects meeting all eligibility criteria will be randomized (1:1) in a double-blind manner to receive maintenance therapy with either lenalidomide or placebo up to disease progression. The randomization procedure will be accomplished by a validated interactive voice response system (IVRS). Subjects will be stratified at randomization by: 1) their response to second-line induction therapy (PR, nPR, CRi or CR versus MRD-negative CR); 2) age (≤ 70 versus > 70 years); and 3) presence of at least one of the following poor prognostic factors: 11q deletion, 17p deletion, unmutated IgVH or β2M > 4.0 mg/L (Yes versus No versus Unknown).

Maintenance Therapy

Study treatment for each subject begins on the same day the subject undergoes randomization. Study visits and serial measurements of safety and efficacy during maintenance therapy will be performed as outlined in Table 2. Lenalidomide is administered orally. Subjects will receive lenalidomide 2.5 mg once daily on Days 1 through 28 of the first 28-day cycle. If the 2.5 mg dose is well tolerated (subject does not experience any Grade 3 or 4 study drug-related toxicities or any other toxicity [Grade 1 or 2] found to be unacceptable by the investigator or the subject), subjects should be escalated starting at the second cycle to 5 mg once daily on Days 1 through 28 of each 28-day cycle up to disease progression ~~or~~ [redacted] If a subject develops a Grade 1 or 2 adverse event, the drug may be interrupted until resolution, however the subject must complete one full cycle at the 2.5 mg dose level prior to escalation to the 5 mg dose level.

Subjects who complete 5 continuous cycles at the 5 mg dose level without experiencing any Grade 3 or 4 study drug-related toxicities and without experiencing any other toxicity (Grade 1 or 2) found to be unacceptable by the investigator may be escalated to 10 mg once daily on Days 1 through 28 of each 28-day cycle up to disease progression [redacted]

Dose interruptions/reductions are permitted for Grade 1 or 2 adverse events at the investigator's discretion. A guideline for the reduction of the dose of lenalidomide for dose-limiting toxicity (DLT) is provided (see Section 10.2.1). Dose re-escalation is permitted if the subject is able to complete 2 full cycles at the reduced dose level without experiencing a DLT or other toxicity deemed to be unacceptable by the investigator or subject. In the event the dose reduction is implemented due to Grade 4 neutropenia, subjects may be re-escalated after one full cycle at the lower dose level if the neutropenia resolves to a Grade 2 or better by the end of the cycle and no other DLT is observed. If that dose level is again not tolerated, the subject should be de-escalated to the dose below and remain at that tolerated dose level for the rest of the study.

Subjects randomized to the lenalidomide treatment arm will continue to receive study lenalidomide maintenance therapy until PD develops [redacted] Progressive disease is characterized by at least one of the following:

- Lymphadenopathy. Progression of lymphadenopathy discovered by physical examination. Disease progression occurs if one of the following events is observed:

- Appearance of any new lesion such as enlarged lymph nodes (> 1.5 cm), splenomegaly, hepatomegaly or other organ infiltrates.
- An increase by 50% or more in greatest determined diameter of any previous site.

- An increase in the previously noted enlargement of the liver or spleen by 50% or more or the de novo appearance of hepatomegaly or splenomegaly.
- An increase in the number of blood lymphocytes by 50% or more with at least 5,000 B lymphocytes per µL.
- Transformation to a more aggressive histology (eg, Richter's syndrome). Whenever possible, this diagnosis should be established by lymph node biopsy.
- Occurrence of cytopenia (neutropenia, anemia or thrombocytopenia) attributable to CLL
- During therapy: cytopenias may occur as a side effect of many therapies and should be assessed according to Table 4. During therapy, cytopenias cannot be used to define disease progression.
- Post treatment: The progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of hemoglobin levels by more than 2 g/dL or to less than 10 g/dL, or by a decrease of platelet counts by more than 50% or to less than 100,000/µL, which occurs at least 3 months after treatment, defines disease progression, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells.

Tumor response, including PD, will be assessed according to the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) guidelines for the diagnosis and treatment of chronic lymphocytic leukemia [redacted]. The severity of AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0 with modifications as noted in Section 10.2.1 of the protocol.

Local hematology and chemistry tests will be performed for patient management/treatment decisions.

Bone marrow aspirate and biopsy specimens obtained from each subject will be reviewed centrally prior to randomization. All repeat bone marrow aspirate and biopsy assessment will be completed at the discretion of the investigators and assessed locally. The bone marrow aspirate and biopsy assessment is removed as part of protocol amendment #10.

The CT scans of the chest, abdomen and pelvis will be performed for all subjects at baseline. All repeat CT scan assessment will be completed at the discretion of the investigator and assessed locally. The CT scan assessment is removed as part of protocol amendment #10.

Amendment #11:

Subjects currently on lenalidomide treatment will discontinue lenalidomide treatment immediately and complete the Treatment Discontinuation assessment. The subjects will then transition to the survival follow-up period.

Prophylaxis for Tumor Lysis Syndrome (TLS), thromboembolism and infection and treatment of tumor flare reaction (TFR)

TLS prophylaxis, comprising of oral hydration and allopurinol 300 mg/day will be initiated 3 days prior to starting maintenance therapy and for a minimum of the first treatment cycle at

each dose level for those subjects entering the study with a PR to their second-line induction therapy. Subjects with a known allergy to allopurinol and a PR will be excluded from the study. Please refer to Section 10.2.1 for further guidance on allopurinol modification in the event of an adverse event. If a subject is taking allopurinol for a condition other than for TLS prophylaxis, the subject should be continued on the allopurinol prescribed by their physician and the dose titrated to 300 mg/day. If, at any time, the allopurinol being taken for reasons other than TLS prophylaxis is discontinued and prophylaxis is still required per protocol, the subject should be administered commercial allopurinol. To maintain fluid intake, subjects must be instructed to drink 8 to 10 eight ounce (240 mL) glasses of water each day for the first 14 days of Cycle 1 and the first cycle of each dose escalation. Hydration levels should be adjusted according to age and clinical status, and lowered if the subject's cardiovascular status indicates the possibility of volume overload. At the investigator's discretion, allopurinol prophylaxis may be omitted for subjects entering the study with a CR; however subjects must be advised of the need for adequate hydration as outlined above.

Grade 1 TFR may be treated with non-steroidal anti-inflammatory drugs (NSAIDs) (ie, ibuprofen 400-600 mg orally every 4-6 hours as needed) and TFR ≥ Grade 2 should be treated with corticosteroids. Narcotic analgesics may be added as needed for pain control in subjects experiencing ≥ Grade 2 tumor flare.

Subjects will be monitored for TLS and TFR on Days 1, 8 and 15 for cycle 1. Monitoring for TLS and TFR will continue on every 28 days thereafter and as clinically indicated.

It is recommended that subjects receive low dose aspirin (75 mg to 100 mg) as prophylactic anti-thrombotic treatment while on study drug, however the use of aspirin should only be implemented after careful evaluation of the hemorrhagic risk and determination that the subject is at limited risk. The investigator may use other anti-coagulation prophylactic therapies (ie, low-molecular weight (LMW) heparin, warfarin, etc.) at their discretion based on the subjects pre-disposing risk factors for thromboembolism (ie, subjects with a history of a thromboembolic event and/or taking a concomitant medication associated with an increased risk for a thromboembolic event and/or known hypercoagulable state regardless of thromboembolic history).

Aspirin should be interrupted if the platelet count drops below 50,000/µL.

Prophylactic antibiotics should be considered in patients with neutropenia. In addition, subjects who were on prophylactic treatment for infection while on alemtuzumab therapy should continue prophylactic treatment for at least 6 months following the discontinuation of alemtuzumab therapy and can be enrolled into the study while continuing prophylactic therapy. Subjects with an active infection requiring systemic antibiotics and subjects with a systemic infection that has not resolved > 2 months prior to initiating lenalidomide treatment in spite of adequate anti-infective therapy are excluded from entering the study.

Treatment and Dose Modification for Tumor Lysis Syndrome (TLS)

Subjects meeting criteria of laboratory TLS or ≥ Grade 1 TLS according to the Cairo-Bishop definition and grading system should be treated as follows:

- Subjects must be hospitalized for ≥ Grade 1 TLS. For laboratory TLS, hospitalization is left to the investigator's discretion.
- The following should be provided: vigorous hydration and appropriate therapy (ie, rasburicase where available) as needed to reduce hyperuricemia, until correction of electrolyte abnormalities.
- In cases of laboratory TLS and Grade 1 TLS, lenalidomide will be continued at the same dose without interruption or dose reduction. Dose escalation to the next

consecutive dose level will be permitted when laboratory TLS is resolved and Grade 1 TLS is resolved to Grade 0.

- Subjects with ≥ Grade 2 TLS will have their dose interrupted and will resume lenalidomide at the next lower dose when electrolyte abnormalities are corrected (ie, Grade 0) as specified in the Dose Modification and Interruption section of the protocol. If lenalidomide is resumed prior to the start of the subsequent cycle, a chemistry test should be performed every other day for the first week following initiation of lenalidomide.
- When those subjects that have been dose reduced complete two full cycles without meeting criteria for laboratory TLS or ≥ Grade 1 TLS or experiencing toxicities, re-escalation to their maximum dose level or to the next higher dose level is permitted.

A total of 320 subjects will be enrolled (160 subjects/treatment arm) in order to detect a 61.3% improvement (hazard ratio of 0.62) in median OS and PFS in the lenalidomide treatment group compared to placebo-treated subjects with 80% statistical power (see Section 16). Enrollment will close once 320 subjects are randomized or 160 adjudicated PFS events are reached, whichever comes first.

Please refer to Figure 1 for an overall summary of the study design.

Analysis and Reporting:

The final analysis on OS will be performed and reported when 160 subjects have died (ie, when full information necessary to have 80% power for OS is achieved).

Data Monitoring Committee

An external independent Data Monitoring Committee will evaluate safety and efficacy data in an ongoing, periodic manner to assess benefit-to-risk considerations. Since the study will be unblinded, the Data Monitoring Committee will not be utilized beginning with protocol amendment #10. Safety reviews will be performed by Celgene annually for the remainder of the study.

Response Adjudication Committee

An independent Response Adjudication Committee will perform a blinded, independent assessment of response (including the development of PD) prior to the interim analysis database lock. Since the placebo arm is discontinued, the Response Adjudication Committee will not be utilized beginning with protocol amendment #10.

Number of planned subjects: 320 (160 subjects per treatment arm)

Enrollment will close once 320 subjects are randomized or 160 adjudicated PFS events are reached, whichever comes first.

Study Population

Key Inclusion Criteria

1. Must understand and voluntarily sign an informed consent form.
2. Age ≥ 18 years at the time of signing the informed consent form.
3. Must be able to adhere to the study visit schedule and other protocol requirements.
4. Must have a documented diagnosis of B-cell CLL (IWCLL guidelines for the diagnosis and treatment of chronic lymphocytic leukemia, [redacted]).
5. Must have been treated with one of the following in first and/or second line:

- a purine analog-containing regimen
- a bendamustine-containing regimen
- an anti-CD20 antibody-containing regimen
- a chlorambucil-containing regimen
- an alemtuzumab-containing regimen (for those subjects with a 17p deletion)

6. Must have achieved a minimum response of partial response (PR, nPR, CRi, CR, and MRD-negative CR) (IWCLL guidelines for the diagnosis and treatment of chronic lymphocytic leukemia, [redacted] Appendix 22.4) following completion of second-line induction therapy prior to randomization (documentation of response status must be available). Second-line induction therapy must be documented to have been of sufficient duration.
7. Must have completed last cycle of second-line induction no less than 8 weeks (56 days) and no greater than 20 weeks (140 days) prior to randomization.
8. Must have an Eastern Cooperative Oncology Group (ECOG) performance status score of ≤2.
9. Females of childbearing potential (FCBP)† must:
   - Have two negative medically supervised pregnancy tests prior to starting of study therapy. She must agree to ongoing pregnancy testing during the course of the study, and after end of study therapy (see specifics in Appendix 22.6). This applies even if the subject practices complete and continued sexual abstinence.
   - Either commit to continued abstinence from heterosexual contact (which must be reviewed on a monthly basis) or agree to use, and be able to comply with, effective contraception without interruption, 28 days prior to starting study drug, during the study therapy (including dose interruptions), and for 28 days after discontinuation of study therapy, (see specifics in Appendix 22.6).
10. Male subjects must:
    - Commit to continued abstinence from heterosexual contact or agree to use a condom during sexual contact with a FCBP, even if they have had a vasectomy, throughout study drug therapy, during any dose interruption, and after cessation of study therapy (See specifics in Appendix 22.6).
    - Agree to not donate semen during study drug therapy and for a period after end of study drug therapy (see specifics in Appendix 22.6).
11. All subjects must:
    - Have an understanding that the study drug could have a potential teratogenic risk.

† Definition found in appendices

- Agree to abstain from donating blood while taking study drug therapy and following discontinuation of study drug therapy (See specifics in Appendix 22.6).
- Agree not to share study medication with another person.
- All subjects must be counseled about pregnancy precautions and risks of fetal exposure (See Appendix 22.6).

Key Exclusion Criteria

1. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
2. Active infections requiring systemic antibiotics.
3. Systemic infection that has not resolved > 2 months prior to initiating lenalidomide treatment in spite of adequate anti-infective therapy
4. Autologous or allogeneic bone marrow transplant as second-line therapy.
5. Pregnant or lactating females.
6. Systemic treatment for B-cell CLL in the interval between completing the last cycle of second-line induction therapy and randomization.
7. Participation in any clinical study or having taken any investigational therapy for a disease other than CLL within 28 days prior to initiating maintenance therapy.
8. Known presence of alcohol and/or drug abuse.
9. Central nervous system (CNS) involvement as documented by spinal fluid cytology or imaging. Subjects who have signs or symptoms suggestive of leukemic meningitis or a history of leukemic meningitis must have a lumbar puncture procedure performed within two weeks prior to randomization.
10. Prior history of malignancies, other than CLL, unless the subject has been free of the disease for ≥5 years. Exceptions include the following:
    - Basal cell carcinoma of the skin
    - Squamous cell carcinoma of the skin
    - Carcinoma *in situ* of the cervix
    - Carcinoma *in situ* of the breast
    - Incidental histologic finding of prostate cancer (tumor-nodes-metastasis [TNM] stage of T1a or T1b)
11. History of renal failure requiring dialysis.
12. Known Human Immunodeficiency Virus (HIV), active Hepatitis B Virus (HBV) and/or active Hepatitis C Virus (HCV) infection.
13. Prior therapy with lenalidomide.
14. Evidence of TLS per the Cairo-Bishop definition of laboratory TLS (Appendix 22.5) (subjects may be enrolled upon correction of electrolyte abnormalities).
15. Any of the following laboratory abnormalities:
    - Calculated (method of Cockroft-Gault) creatinine clearance of <60 mL/min
    - Absolute neutrophil count (ANC) < 1,000/µL (1.0 X 10^9/L)
    - Platelet count < 50,000/µL (50 X 10^9/L)
    - Serum aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) or alanine transaminase (ALT)/serum glutamate pyruvate transaminase (SGPT) > 3.0 x upper limit of normal (ULN)

- Serum total bilirubin > 2.0 mg/dL (with the exception of Gilbert's Syndrome)

16. Grade 4 rash due to prior thalidomide treatment.
17. Uncontrolled hyperthyroidism or hypothyroidism.
18. Venous thromboembolism within one year.
19. ≥ Grade-2 neuropathy.
20. Uncontrolled autoimmune hemolytic anemia or thrombocytopenia.
21. Disease transformation (active) (ie, Richter's Syndrome, prolymphocytic leukemia).
22. Known allergy to allopurinol for subjects assessed with PR following their second-line induction therapy.
23. Prisoners.
24. More than 2 prior lines of CLL therapy.

Investigational product, dosage and mode of administration: Celgene Corporation will supply lenalidomide 2.5 mg, 5 mg, and 10 mg capsules for oral administration. Subjects dose reduced to 7.5 mg dose level (as outlined in Section 10.2.1) will receive one 5.0 mg capsule and one 2.5 mg capsule daily.

Study drug will be packaged in bottles containing study capsules for 28 days.

Subjects currently on lenalidomide treatment will discontinue lenalidomide treatment immediately. Celgene will discontinue supply of lenalidomide as a part of Protocol Amendment #11.

Assessments:

Efficacy:

- Survival/Date of death

Safety:

- Clinical laboratory evaluations
- Pregnancy testing
- [redacted]
- AEs by NCI CTCAE Version 3.0, with modifications recommended by the IWCLL guidelines for the diagnosis and treatment of chronic lymphocytic leukemia [redacted] (Appendix 22.4)
- Second primary malignancies will be monitored as events of interest and should be included as part of the assessment of adverse events throughout the course of the study. Investigators are to report any second primary malignancies as serious adverse events regardless of causal relationship to study drug, occurring at any time for the duration of the study, from the time of signing the informed consent up to and including the survival follow-up phase

[redacted]

- [redacted]
- [redacted]

Statistical Analysis:

Overview:

The objective of the statistical analysis will be to compare the efficacy and safety of lenalidomide versus placebo as maintenance therapy in subjects with relapsed or refractory B-cell chronic lymphocytic leukemia (CLL) having achieved PR or better after second-line therapy.

Overall Survival (OS) will be the primary endpoint for the study following protocol amendment #10.

Sample Size:

For OS, a 61.3% improvement in median survival from randomization, from 3 years for placebo to 4.84 years on lenalidomide is considered clinically relevant. The OS distribution is assumed to be exponential with a constant failure (hazard) rate. At the conclusion of the study a two-sided log-rank test with an overall significance level of 0.025 would have 80% power to detect a hazard rate ratio of 0.62. To ensure timely completion of the study, 320 subjects will be enrolled, 160 in each treatment arm. Enrollment will close once 320 subjects are randomized or 160 adjudicated PFS events are reached, whichever comes first.

Demographic, Disposition, Study Medication:

The baseline characteristics of subjects enrolled in each arm will be summarized. An accounting will be made of the study course for all subjects who received study drug for each arm and, in particular, the number of subjects who expired or withdrew during treatment will be specified and reasons for withdrawal categorized.

Efficacy Analysis:

Efficacy analyses will be performed on the intent-to-treat (ITT) population that includes all subjects randomized.

Overall Survival (OS) will be the primary endpoint for the study following protocol amendment #10.

Exploratory analyses will be performed to investigate relationships between biomarker expression/cytogenetic characteristics, age and overall survival. Cytogenetic response will be evaluated in that subset of subjects who have follow-up cytogenetics.

Safety Analysis:

All subjects who receive at least 1 dose of study medication will be included in the safety analyses. AEs, clinical laboratory information, and concomitant medications will be tabulated and summarized. Subject incidence rates of all AEs (including serious, Grade 3, Grade 4, treatment-related [with and without discontinuation] and events requiring the discontinuation of investigational product), will be tabulated by system class, preferred term, and severity using Medical Dictionary for Regulatory Activities (MedDRA) terms and NCI CTCAE Version 3.0 severity grades with modifications. (Section 10.2.1). Time to first dose reduction will be summarized. The adverse event of infection will also be analyzed according to the grading system as recommended by the IWCLL guidelines for the diagnosis and treatment of CLL [redacted] (Appendix 22.4).

Death and clinically important AEs (including tumor flare, tumor lysis, second primary malignancies, and thrombosis) will also be summarized.

All other measurements will be summarized using means, standard deviations, medians, minimum, and maximum. Graphical displays will be provided where useful in the interpretation of results.

Table 2: Schedule of Assessments

	Maintenance Therapy				After Treatment Discontinuation
Procedure[a]	**Screening ≤ 28 days prior to Day 1**	**Study Day 1**	**Every 28 days (4 weeks)**	**Tx discontinuation**	**Survival Follow-up~~post disease progression~~:[b] Every 24 weeks (+/- 7 days)**
ICF/Inclusion/Exclusion	X	--	--	--	--
Medical history	X	--	--	--	--
Pregnancy test[c]	X[c]	--	X[c]	X[c]	--
Pregnancy and risks counseling[d]	X[d]	X[d]	X[d]	X[d]	--
ECOG Performance Status	X	X	--	X	--
Evaluation of constitutional symptoms	X	X	--	X	--
Physical examination to assess lymphadenopathies, spleen, and liver[e]	X	X	--	X	--
Vital signs including weight[f]	X	X	--	X	--
Hematology[g]	X	X	X	X	--
Chemistry[h]	X	X	X	X	--
Calculated creatinine clearance (method of Cockroft-Gault)	X	--	--	--	--
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Direct Antiglobulin Test (DAT)[j]	X	--	--	--	--
ECG (12 lead)[k]	X	X	--	X	--
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 2 Schedule of Assessments (Continued)

	Maintenance Therapy				After Treatment Discontinuation
Procedure[a]	**Screening ≤28 days prior to Day 1**	**Study Day 1**	**Every 28 days (4 weeks)**	**Tx discontinuation**	**Survival Follow-up~~post disease progression~~:[b] Every 24 weeks (+/- 7 days)**
Tumor lysis monitoring and prophylaxis (allopurinol administration) and tumor flare reaction monitoring[n]	X	X	X	--	--
Study drug administration[o]	--	X	X	--	--
Adverse events[b,p]	X	X	X	X	--
Assessment of Second Primary Malignancies[q]	X	X	X	X	X
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assessment of response[r]	--	--	X	X	--
Survival[b]	--	--	--	--	X

ALC = absolute lymphocyte count; ANC = absolute neutrophil count; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CLL = chronic lymphocytic leukemia; CR = complete response; CRi = complete response with incomplete bone marrow recovery; CRF = case report form; CT = computed tomography; DAT = direct antiglobulin test; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in-situ hybridization; HCT = hematocrit; HGB = hemoglobin; ICF = informed consent form; NK = natural killer; nPR = nodular partial response; PD = progressive disease; PR = partial response; SAE = serious adverse event; WBC = white blood cell; ZAP-70 = Zeta-chain Associated Protein kinase 70

[a] All study procedures should be performed within ± 3 days of the scheduled visit unless otherwise stated.

[b] Subjects who discontinued from the study drug will be followed for survival, subsequent CLL therapies, response to next therapy and progression following next therapy, and second primary malignancies at each of these visits. Subjects will be followed until all subjects in the study have been followed for at least 5 years from last subject randomized, October 2020, (or have died/become lost to follow-up before 5 years).

[c] Females of childbearing potential (FCBP) must have a medically supervised pregnancy test (serum or urine with sensitivity of at least 25 mIU/mL). FCBP must have 2 negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 10 to 14 days prior to the start of study drug and the second pregnancy test must be performed within 24 hours prior to the start of study drug. The patient may not receive study drug until the Investigator has verified that the results of these pregnancy tests are negative (see Appendix 22.6). **For additional information on the frequency and schedule of pregnancy testing, see the document entitles "Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods" in Appendix 22.6. For requirements regarding: 1) counselling and education of patients, including the reading of**

the "Lenalidomide Information Sheet" by the patient; 2) reliable contraception methods; and 3) retention of Risk Management Plan documents concerning the pregnancy prevention program, see Appendix 22.6.

[d] All male and FCBP patients must be counselled about pregnancy precautions and risks of fetal exposure. All patients must also be counselled against sharing study drug and donating blood during and within 28 days of discontinuing study drug (see Appendix 22.6. for frequency).

[e] Physical examination of lymphadenopathies, the spleen and liver will be performed at screening, Study Day 1, and at the treatment discontinuation visit. Lymph node evaluation will record the diameter, in two dimensions, of the largest palpable nodes in each of the following sites: cervical, axillary, supraclavicular, inguinal, and femoral.

[f] Vital signs include: temperature, pulse, blood pressure, weight, and height (height to be measured at baseline only)

[g] Hematology includes WBC, HGB, HCT, platelet count, ANC, and ALC.

[h] Chemistry includes potassium, calcium, phosphorus, creatinine, alkaline phosphatase, total bilirubin, AST/SGOT, ALT/SGPT, and uric acid.

[i] β2M will be analysed during screening and, in selected sites, after one and two years of treatment and later if appropriate.

[j] DAT (direct antiglobulin test) will be performed at screening and analyzed at the central laboratory. The DAT test must be repeated if the investigator suspects haemolytic anemia during the course of the study.

[k] ECG will be performed at baseline and at treatment discontinuation and interpreted locally.

[l] Peripheral blood for FISH, ZAP 70, IgV_H mutational status analyses and storage will be drawn during screening and analysed at a central laboratory.

[m] NK and T cell analyses will be performed at screening.

[n] Tumor lysis prophylaxis, consisting of oral hydration and allopurinol 300 mg/day, will be administered for **3 days prior to starting treatment** and for at least the first cycle of each dose level. At the investigator's discretion, allopurinol prophylaxis may be omitted for subjects entering the study with a CR; however subjects must be advised of the need for adequate hydration.

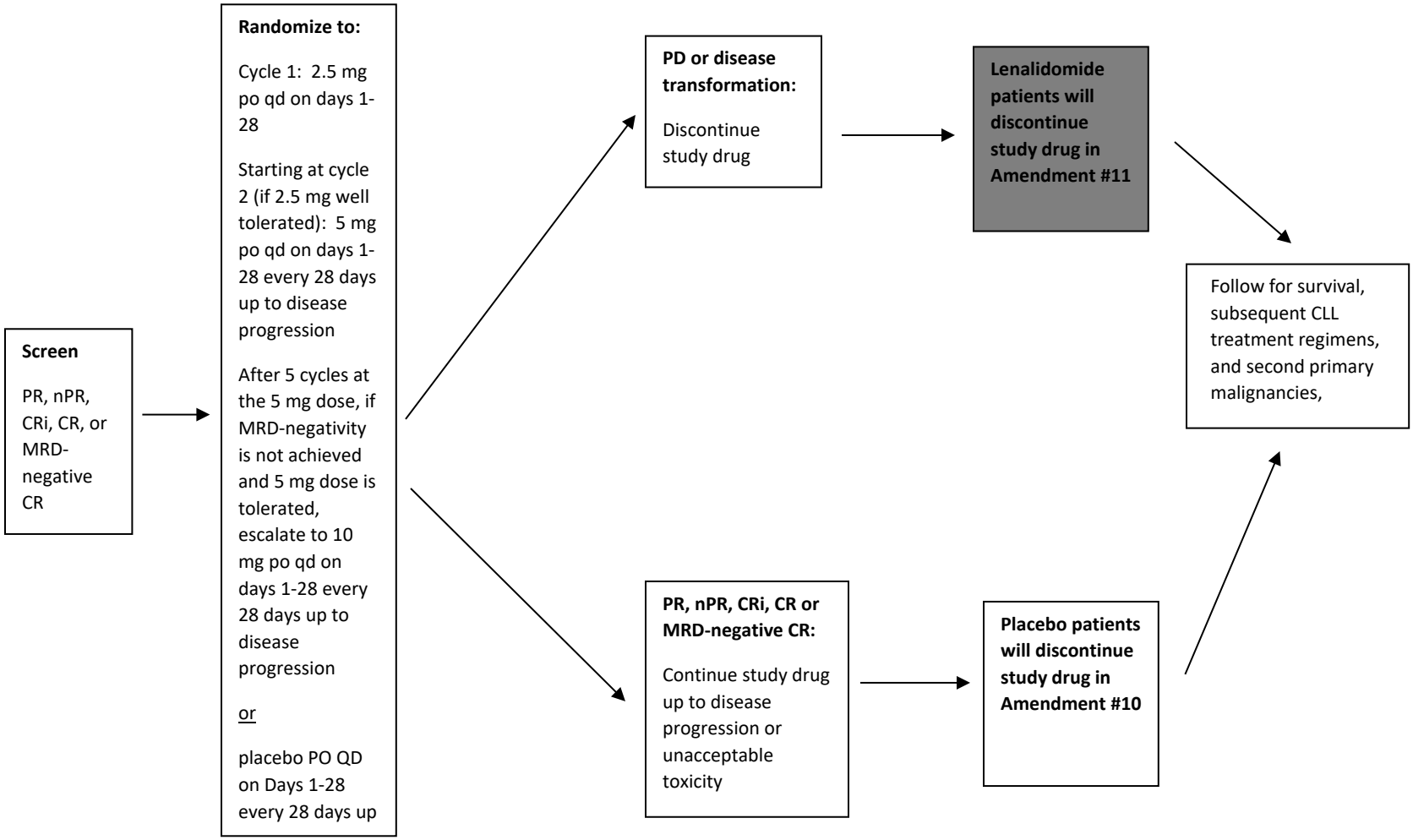
[o] Study drug to be dispensed in 28-day cycles. Subjects should be instructed to return the bottle every 28 days.

[p] Adverse events that lead to study discontinuation should be followed until resolution or stabilization. Serious adverse events should be monitored for 30 days after treatment discontinuation. All SAEs should be followed until resolution or stabilization. Any SAE deemed by the investigator to be related to study drug should be reported and followed until resolution.

[q] Second primary malignancies will be monitored as events of interest and must be reported as serious adverse events. This includes any second primary malignancy, regardless of causal relationship to study drug, occurring at any time for the duration of the study, from the time of signing the informed consent up to and including the survival follow-up period. Subjects will be followed until all subjects in the study have been followed for at least 5 years from randomization (or died/become lost to follow-up before 5 years). Events of second primary malignancy 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 a serious adverse event (eg, any confirmatory histology or cytology results, X-rays, CT scans, etc.).

[r] Investigators to provide assessment of CR, CRi, nPR, PR, and PD based on laboratory, physical exam, and if appropriate bone marrow aspirate/biopsy and CT scan findings. To confirm a complete response, subjects must have maintained no evidence of disease for $\geq$ 8 weeks and partial response must be maintained for $\geq$8 weeks as per the IWCLL guidelines for the diagnosis and treatment of chronic lymphocytic leukemia (Hallek, 2008).

Figure 1: Schema of Events



CLL= chronic lymphocytic leukemia, CR = complete response, CRi = complete response with incomplete bone marrow recovery, MRD = Minimal residual disease; nPR = nodular partial response, PO = oral, PD = progressive disease, PR = partial response, QD = every day

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5. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 3: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse event
ALC	Absolute lymphocyte count
ALT (SGPT)	Alanine transaminase (serum glutamate pyruvic transaminase)
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST (SGOT)	Aspartate transaminase (serum glutamic oxaloacetic transaminase)
ATC	Anatomic Therapeutic Chemical
β2M	Beta-2 Microglobulin
β –HCG	Beta-human chorionic gonadotropin hormone
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Confidence Interval
CLL	Chronic lymphocytic leukemia
Clb	Chlorambucil
CNS	Central nervous system
CR	Complete response
Cri	Complete response with incomplete bone marrow recovery
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DAT	Direct antiglobulin test
DCF	Data Clarification Form
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency

Abbreviation or Specialist Term	Explanation
EU	European Union

Table 3: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
F	Fludarabine
FC	Fludarabine and Cyclophosphamide
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
FISH	Fluorescence in Situ Hybridization
GClb	Obinutuzumab and Chlorambucil
GCP	Good Clinical Practice
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HGB	Hemoglobin
HCT	Hematocrit
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgVh	Immunoglobulin Heavy-chain Variable-region
IL-6	Interleukin 6
IL-10	Interleukin 10
IMiD	Immunomodulatory drug
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous(ly)
IVRS	Interactive Voice Response System
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
LMW	Low-molecular weight
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or Specialist Term	Explanation
MRD	Minimal residual disease
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events

Table 3: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
NCI-WG	National Cancer Institute Working Group criteria for chronic lymphocytic leukemia
NK cells	Natural killer cells
nPR	Nodular partial response
NSAID	Non-steroidal anti-inflammatory drug
ORR	Overall response rate
OS	Overall Survival
PCR	Pentostatin, cyclophosphamide, and rituximab
PD	Progressive disease
PFS	Progression free survival
PFS2	Progression free survival 2
PR	Partial Response
RClb	Rituxan and Chlorambucil
RIC	Reduced intensity conditioning
SAE	Serious adverse event
SD	Stable disease
SGOT	Serum-Glutamic-Oxaloacetic Transaminase
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reaction
TFR	Tumor flare reaction
TLS	Tumor lysis syndrome
TNF α	Tumor necrosis factor alpha
TNM	Tumor-nodes-metastasis
ULN	Upper limit of normal
US	United States

Abbreviation or Specialist Term	Explanation
VEGF	Vascular endothelial growth factor
VTE	Venous thromboembolism
WBC	White blood cell count
WG	Working Group

Table 3: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
WHO	World Health Organization
ZAP 70	Zeta-Chain-Associated Protein Kinase 70

7. STUDY OBJECTIVES

7.1. Primary Objective

- To compare the efficacy of lenalidomide *versus* placebo maintenance therapy

7.2. Secondary Objective

- To evaluate the safety of lenalidomide *versus* placebo maintenance therapy

8. STUDY ENDPOINTS

8.1. Primary

- Overall Survival (OS)

8.2. Secondary

- Safety [type, frequency, and severity of AEs and relationship of AEs to lenalidomide]
- Progression-Free Survival 2 (PFS2)

9. INVESTIGATIONAL PLAN

9.1. Overall Study Design

CC-5013-CLL-002 is a phase 3, multicenter, randomized, placebo-controlled, parallel-group study that will compare the efficacy and safety of oral lenalidomide maintenance therapy to that of placebo in subjects with B-cell CLL who achieved at least partial response (PR) with second-line therapy. The primary efficacy objective of this study is to demonstrate superiority of lenalidomide over placebo in prolonging OS due to continued therapy, for all subjects, including subjects with or without poor prognostic factors, subjects of various ages and subjects with PR, nodular partial response (nPR), complete response with incomplete bone marrow recovery (CRi), complete response (CR), and minimal residual disease (MRD)-negative CR. All subjects randomized to the lenalidomide arm, including those subjects who do not improve their response (PR, nPR, CRi, or CR) and subjects who do not have the opportunity to improve their response further (MRD-negative CR) will be treated up to disease progression [redacted] with the objective to demonstrate prolongation of OS.

Amendment #11:

Subjects currently on lenalidomide treatment will discontinue lenalidomide treatment immediately and complete the Treatment Discontinuation assessment. The subjects will then transition to the survival follow-up period.

Eligible subjects must have been treated with a purine analog-, a bendamustine-, an anti-CD20 antibody-, or a chlorambucil-based regimen in first and/or second line and must have achieved at least PR to second-line induction therapy of sufficient duration. Alemtuzumab- containing regimens will also be allowed for those patients with 17p deletion. Subjects who achieve stable disease (SD) only or who develop progressive disease (PD) at any time during induction therapy will not be eligible for participation in this study.

Approximately, three hundred twenty (320) subjects with PR, nPR, CRi, CR or MRD-negative CR will be enrolled and randomized (1:1) into two arms: placebo daily or lenalidomide 2.5 mg daily on days 1-28 of the first cycle. If the 2.5 mg dose level is well tolerated, escalation to 5 mg daily on days 1-28 of each 28-day cycle is permitted starting with the second cycle. If a subject develops a Grade 1 or 2 adverse event, the drug may be interrupted until resolution, however the subject must complete one full cycle at the 2.5 mg dose level prior to escalation to the 5 mg dose level. For those subjects who tolerate the 5 mg dose without unacceptable toxicity, escalation to 10 mg daily on days 1-28 of each 28-day cycle after 5 continuous cycles at 5 mg will be permitted. Each treatment arm will be stratified according to 1) the response to second-line induction therapy (PR, nPR, CRi or CR versus MRD-negative CR); 2) age ($\leq$ 70 versus > 70 years); and 3) presence of at least one of the following poor prognostic factors: 11q deletion, 17p deletion, unmutated IgV_H or $\beta 2M$ > 4.0 mg/L (Yes versus No versus Unknown).

The subjects randomized to the lenalidomide treatment will continue to receive lenalidomide up to PD [redacted]. For those subjects who discontinue therapy for reasons other than PD (ie, unacceptable toxicity) they will transition to the survival follow-up period.

Subjects who discontinued from the study drug will be followed every 24 weeks for survival, subsequent CLL therapies, response to next therapy and progression following next therapy, and second primary malignancies. Subjects will be followed until all subjects in the study have been followed for at least 5 years from the last randomization, October 2020, (or have died/become lost to follow up before 5 years).

Screening:

Potential study subjects will be screened for protocol eligibility within 28 days prior to randomization as outlined in Table 2. Please refer to Figure 1.

During the screening process for potentially protocol-eligible subjects, complete blood counts (CBCs), serum chemistries, thyroid function tests, quantitative immunoglobulin tests, a 12-lead electrocardiogram (ECG), physical exam to assess lymphadenopathies, the spleen and the liver, vital signs (with weight), Eastern Cooperative Oncology Group (ECOG) performance status, and evaluation of constitutional symptoms will be performed.

Bone marrow biopsies and aspirates are to be performed on all subjects at screening. A central review of the bone marrow aspirate and biopsy specimens will be performed to confirm disease status. Subjects who develop PD during screening will not be eligible to enroll into this study. Peripheral blood will be sent to a central laboratory for flow cytometry for all subjects for disease diagnosis confirmation (by immunophenotyping), to perform immune cell (NK and T cell) analyses and for subjects entering the study with a CR for determination of MRD status. If peripheral blood is MRD negative, a bone marrow flow cytometry will be implemented. If subjects enter the study with MRD negativity, the disease diagnosis will be confirmed based on prior flow cytometry (documentation needed).

A peripheral blood sample for a direct antiglobulin test (DAT) will be collected and analyzed at a central laboratory.

Before randomization, subjects will be tested for cytogenetics by FISH, IgV_H mutational status, and β2M. The β2M test will be performed during screening using a peripheral blood sample and analyzed at a central laboratory.

FISH and IgV_H testing will be performed prior to second line, during second line, in the interval between second-line therapy and screening or during the screening period using a peripheral blood sample. Because test results cannot be obtained during screening or between second line and screening in some subjects who achieve a good response due to the limited number of remaining CLL cells, we recommend conducting the FISH and IgV_H tests preferably prior to second line or during second line.

Samples for FISH and IgV_H will be analyzed at a central laboratory.

If tests do not yield results, subjects can be randomized and stratified based on historical data.

Those subjects for whom results were not obtainable pre-randomization and for whom no historical data were available will be enrolled and grouped separately.

An additional peripheral blood sample will be collected at baseline and stored at -70° at a central laboratory until the completion of the study; subjects will be re-consented if additional testing is to be performed.

Computed tomography (CT) scans of the chest, abdomen, and pelvis will be performed at baseline for all subjects to document the subject's status (PR or CR).

If, during the screening period, the subject has a correctable event that prevents randomization and the event cannot be corrected within the 28 day screening period, the subject may be re-screened; however, the CT scans and bone marrow aspirate and biopsy will not need to be repeated if those tests were implemented within 56 days prior to randomization and the subject's clinical status remains the same.

Females of childbearing potential (FCBP) must have two negative pregnancy tests performed at the study site prior to initiating lenalidomide therapy. The first pregnancy test will be performed within 10-14 days prior to randomization and the second test within 24 hours prior to starting study drug. FCBP must agree to birth control requirements as outlined in Appendix 22.6 during the following time periods related to this study: 1) for at least 28 days before starting study drug; 2) while participating in the study; and 3) at least 28 days after the treatment discontinuation visit. FCBP must be referred to a qualified provider of contraceptive methods, if needed. Males must commit to continued abstinence from heterosexual contact or agree to use appropriate contraceptive methods during any sexual contact with FCBP during study participation and for at least 28 days following the treatment discontinuation visit as outlined in Appendix 22.6. Male subjects must agree to abstain from donating blood, semen or sperm during study participation and for at least 28 days after the treatment discontinuation visit. Subjects must be counseled about pregnancy precautions and the potential risk of fetal exposure.

Randomization:

Randomization must occur no less than 8 weeks (56 days) and no greater than 20 weeks (140 days) from the last day of the last cycle of second-line induction therapy received by the subject in order for the subject to be eligible for enrollment into this study. Subjects meeting all eligibility criteria will be randomized (1:1) in a double-blind fashion to receive either lenalidomide or placebo. The randomization procedure will be accomplished by a validated interactive voice response system (IVRS) (see Section 10.1.1). Subjects will be stratified at randomization by: 1) their response to second-line induction therapy (PR, nPR, CRi or CR versus MRD-negative CR); 2) age (≤ 70 versus > 70 years); and 3) presence of at least one of the following poor prognostic factors: 11q deletion, 17p deletion, unmutated IgV_H or β2M > 4.0 mg/L (Yes versus No versus Unknown).

Maintenance Therapy:

Study treatment for each subject begins on the same day the subject undergoes randomization. Lenalidomide is administered orally. Subjects will receive lenalidomide 2.5 mg once daily on Days 1 through 28 of the first 28-day cycle. If the 2.5 mg dose is well tolerated (subject does not experience any Grade 3 or 4 study drug-related toxicities or any other toxicity [Grade 1 or 2] found to be unacceptable by the investigator or the subject), subjects should be escalated starting at the second cycle to 5 mg once daily on Days 1 through 28 of each 28-day cycle up to disease progression [redacted]. If a subject develops a Grade 1 or 2 adverse event, the drug may be interrupted until resolution, however the subject must complete one full cycle at the 2.5 mg dose level prior to escalation to the 5 mg dose level.

Subjects who complete 5 continuous cycles at the 5 mg dose level without experiencing any Grade 3 or 4 study drug-related toxicities and without experiencing any other toxicity (Grade 1 or 2) found to be unacceptable by the investigator may be escalated to 10 mg once daily on Days 1 through 28 of each 28-day cycle up to disease progression [redacted]

Dose de-escalation to 7.5 mg from 10 mg and to 5 mg from 7.5 mg and to 2.5 mg from 5 mg and to 2.5 mg every other day from 2.5 mg will be permitted for those subjects who experience a Grade 3 or 4 study drug-related toxicity or any other Grade 1 or 2 toxicity found to be unacceptable by the investigator or subject.

Dose interruptions are also permitted for Grade 1 or 2 adverse events at the investigator's discretion. A guideline for the reduction of the dose of lenalidomide for dose-limiting toxicity (DLT) is provided (see Section 10.2.1).

Dose re-escalation is permitted if the subject is able to complete 2 full cycles at the reduced dose level without experiencing a DLT or other toxicity deemed to be unacceptable by the investigator or subject. In the event the dose reduction is implemented due to Grade 4 neutropenia, subjects may be re-escalated after one full cycle at the lower dose level if the neutropenia resolves to a Grade 2 or better by the end of the cycle and no other DLT is observed. If that dose level is again not tolerated, the subject should be de-escalated to the dose below and remain at that tolerated dose level for the rest of the study.

Study visits and serial measurements of safety and efficacy will be performed as outlined in Table 2.

Females of childbearing potential must have a pregnancy test (conducted by the study site) within 24 hours prior to starting study drug; the subject may not receive study drug until the Investigator has verified that the pregnancy test is negative. Pregnancy testing for FCBP will continue throughout the study as outlined in Table 2 and Appendix 22.6.

Counseling regarding blood, eggs and ovum donation, and contraceptive use and the potential risks of fetal exposure should be performed as outlined in Appendix 22.6.

FCBP should be monitored during the course of the study and after the end of study therapy to:

- Ensure that pregnancy tests are performed during the course of the study and after end of study therapy and are negative (see specifics in Appendix 22.6).
- Ensure the subject continues to practice abstinence or remains on adequate contraception (see specifics in Appendix 22.6).

If a FCBP becomes pregnant, treatment should be stopped and the subject referred to the appropriate physician.

Male subjects should be monitored during the course of the study and after the end of study therapy to:

- Ensure they commit to continued abstinence from heterosexual contact or continue to use a condom during sexual contact with a FCBP.

- If a female partner of a male subject becomes pregnant she should be referred to the appropriate physician.

CBCs will be monitored on Days 1, 8, and 15 of cycle 1, on Day 1 of each cycle thereafter, and at the treatment discontinuation visit. In the event of Grade 4 hematologic toxicity, monitoring of CBCs will continue weekly until resolution to grade 3 or better. It is recommended to utilize myeloid and erythroid growth factors as per the American Society of Clinical Oncology (ASCO) guidelines. The use of myeloid growth factors is encouraged when the absolute neutrophil count (ANC) is less than 1,000/μL.

If a subject develops Grade 4 neutropenia or thrombocytopenia, the drug will be withheld until the toxicity has recovered to Grade 3 or better. The drug may then be restarted at one dose level lower. If the treatment has been withheld and the next cycle is delayed beyond 29 days after day 1 of the prior treatment cycle, then day 1 of the next treatment cycle will be defined as the first day that the treatment is resumed.

Serum chemistries will be performed on Days 1, 8, and 15 of cycle 1, on Day 1 of each cycle thereafter, and at the treatment discontinuation visit.

Scheduled laboratory studies (CBCs, chemistries) will be sent to the site's local laboratory for analysis purposes.

The DAT test must be repeated if the investigator suspects haemolytic anemia and will be analysed centrally during the course of the study.

ECOG Performance Status will be measured at the treatment discontinuation visit.

Evaluation of constitutional symptoms will be performed at the treatment discontinuation visit.

Vitals signs will be monitored at the treatment discontinuation visit. A physical examination to assess in particular lymphadenopathies, spleen and liver will be performed at the treatment discontinuation visit.

An ECG will be performed at the treatment discontinuation visit.

Investigators will assess subjects for response every 28 days and at the treatment discontinuation visit. Investigators will provide an assessment of CR (MRD-negative or MRD-positive), CRi, nPR, PR, and PD based on laboratory, physical exam, and if appropriate local assessments for CT scan findings, flow cytometry and bone marrow aspirate and biopsy. To confirm a CR, subjects must have maintained no evidence of disease for ≥ 8 weeks and PR must be maintained for ≥ 8 weeks as per the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) guidelines for the diagnosis and treatment of chronic lymphocytic leukemia [redacted]

FCBP must have a pregnancy test at the treatment discontinuation visit.

Subjects will receive study maintenance therapy until PD develops; any disease transformation will need to be documented by lymph node biopsies for Richter's syndrome and percent of peripheral blood or bone marrow prolymphocytes for prolymphocytic leukemia. Progressive disease is characterized by at least one of the following:

- Lymphadenopathy. Progression of lymphadenopathy discovered by physical examination. Disease progression occurs if one of the following events is observed:

  - Appearance of any new lesion such as enlarged lymph nodes (> 1.5 cm), splenomegaly, hepatomegaly or other organ infiltrates.
  - An increase by 50% or more in greatest determined diameter of any previous site.
- An increase in the previously noted enlargement of the liver or spleen size by 50% or more or the de novo appearance of hepatomegaly or splenomegaly.
- An increase in the number of blood lymphocytes by 50% or more with at least 5,000 B lymphocytes per µL.
- Transformation to a more aggressive histology (eg, Richter's syndrome). Whenever possible, this diagnosis should be established by lymph node biopsy.
- Occurrence of cytopenia (neutropenia, anemia or thrombocytopenia) attributable to CLL.
- During therapy: cytopenias may occur as a side effect of many therapies and should be assessed according to Table 4. During therapy, cytopenias cannot be used to define disease progression.
- Post treatment: The progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of hemoglobin levels by more than 2 g/dL or to less than 10 g/dL, or by a decrease of platelet counts by more than 50% or to less than 100,000/µL, which occurs at least 3 months after treatment, defines disease progression, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells.

Prophylaxis for TLS, thromboembolism and infection and treatment of tumor flare reaction (TFR):

TLS prophylaxis, comprising of oral hydration and allopurinol 300 mg/day will be initiated 3 days prior to starting maintenance therapy and for a minimum of the first treatment cycle at each dose level for those subjects entering the study with a PR to their second-line induction therapy. Subjects with a known allergy to allopurinol with a response of PR will be excluded from the study. Please refer to Section 10.2.1 for further guidance on allopurinol modification in the event of an adverse event. If a subject is taking allopurinol for a condition other than for TLS prophylaxis, the subject should be continued on the allopurinol prescribed by their physician and the dose titrated to 300 mg/day. If, at any time, the allopurinol being taken for reasons other than TLS prophylaxis is discontinued and prophylaxis is still required per protocol, the subject should be administered commercial allopurinol. To maintain fluid intake, subjects must be instructed to drink 8 to 10 eight ounce (240 mL) glasses of water each day for the first 14 days of cycle 1 and the first cycle of each dose escalation. Hydration levels should be adjusted according to age and clinical status, and lowered if the subject's cardiovascular status indicates the possibility of volume overload. At the investigator's discretion, allopurinol prophylaxis may be omitted for subjects entering the study with a CR; however subjects must be advised of the need for adequate hydration as outlined above.

Grade 1 TFR may be treated with non-steroidal anti-inflammatory drug (NSAIDs) (ie, ibuprofen 400-600 mg orally every 4-6 hours as needed) and TFR ≥ Grade 2 should be treated with

corticosteroids. Narcotic analgesics may be added as needed for pain control in subjects experiencing ≥ Grade 2 tumor flare.

Subjects will be monitored for TLS and TFR on Days 1, 8, and 15 for cycle 1 and the first cycle of each dose escalation. Monitoring for TLS and TFR will continue on Days 1 and 15 for the second cycle of each dose level, at least every 28 days thereafter, and as clinically indicated.

It is recommended that subjects receive low dose aspirin (75 mg to 100 mg) as prophylactic anti-thrombotic treatment while on study drug, however the use of aspirin should only be implemented after careful evaluation of the hemorrhagic risk and determination that the subject is at limited risk. The investigator may use other anti-coagulation prophylactic therapies (ie, low-molecular weight (LMW) heparin, warfarin, etc.) at their discretion based on the subjects pre-disposing risk factors for thromboembolism (ie, subjects with a history of a thromboembolic event and/or taking a concomitant medication associated with an increased risk for a thromboembolic event and/or known hypercoagulable state regardless of thromboembolic history).

Aspirin should be interrupted if the platelet count drops below 50,000/μL.

Prophylactic antibiotics should be considered in patients with neutropenia. In addition, subjects who were on prophylactic treatment for infection while on alemtuzumab therapy should continue prophylactic treatment for at least 6 months following the discontinuation of alemtuzumab therapy and can be enrolled into the study while continuing prophylactic therapy. Subjects with an active infection requiring systemic antibiotics and subjects with a systemic infection that has not resolved > 2 months prior to initiating lenalidomide treatment in spite of adequate anti-infective therapy are excluded from entering the study.

Treatment and Dose Modification for Tumor Lysis Syndrome (TLS):

Subjects meeting criteria of laboratory TLS or ≥ Grade 1 TLS according to the Cairo-Bishop definition and grading system should be treated as follows:

- Subjects must be hospitalized for ≥ Grade 1 TLS. For laboratory TLS, hospitalization is left to the investigator's discretion.
- The following should be provided: vigorous hydration and appropriate therapy (ie, rasburicase where available) therapy as needed to reduce hyperuricemia, until correction of electrolyte abnormalities.
- In cases of laboratory TLS and Grade 1 TLS, lenalidomide will be continued at the same dose without interruption or dose reduction. Dose escalation to the next consecutive dose level will be permitted when laboratory TLS is resolved and Grade 1 TLS is resolved to Grade 0.
- Subjects with ≥ Grade 2 TLS will have their dose interrupted and will resume lenalidomide at the next lower dose when electrolyte abnormalities are corrected (ie, Grade 0) as specified in the Dose Modification and Interruption section of the protocol. If lenalidomide is resumed prior to the start of the subsequent cycle, a chemistry test should be performed every other day for the first week following initiation of lenalidomide.

- When those subjects that have been dose reduced complete two full cycles without meeting criteria for laboratory TLS or ≥ Grade 1 TLS or experiencing toxicities, re-escalation to their maximum dose level or to the next higher dose level is permitted.

The severity of AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0 with modifications. The severity of TLS AEs will be graded according to the Cairo-Bishop grading system.

Amendment #11:

Subjects currently on lenalidomide treatment will discontinue lenalidomide treatment immediately and complete the Treatment Discontinuation assessment. The subjects will then transition to the survival follow-up period.

After Study Discontinuation:

Upon discontinuation of study drug, subjects will be followed every 24 weeks for survival, information on other CLL treatments, response to next therapy and progression following next therapy, and second primary malignancies (reported as SAEs). Subjects will be followed until all subjects in the study have been followed for at least 5 years from the last randomization, October 2020 (or have died/become lost to follow-up before 5 years).

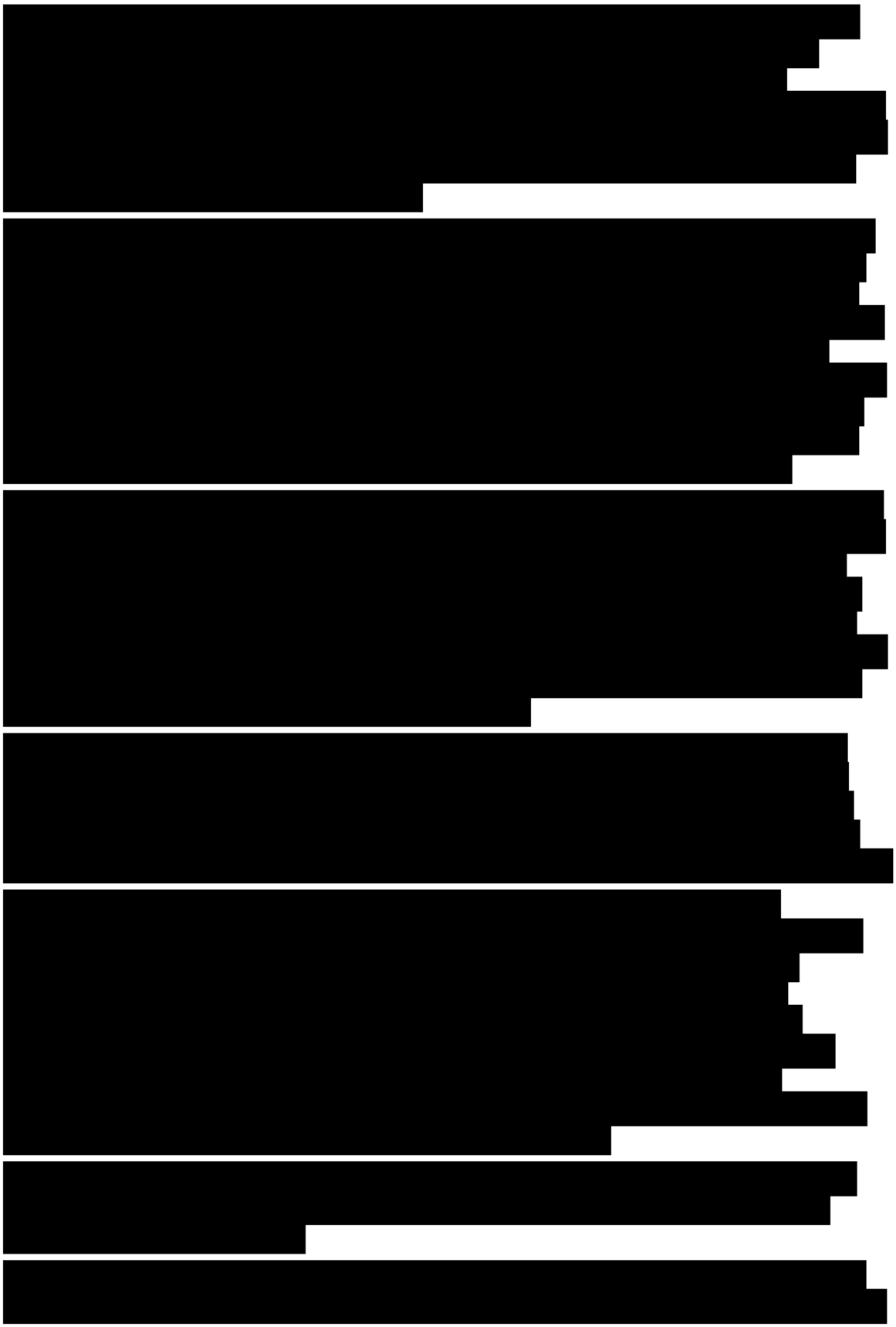
FCBP with regular menstrual cycles discontinued from treatment must have a pregnancy test on day 28 after the treatment discontinuation visit. FCBP with irregular cycles discontinued from treatment must have a pregnancy test on days 14 and 28 after the treatment discontinuation visit.

SAEs will continue to be collected for the first 30 days after the treatment discontinuation visit. Following 30 days post the treatment discontinuation visit, only SAEs related to maintenance therapy will be collected for the study duration. Second primary malignancies must be reported as SAEs. This includes any second primary malignancy, regardless of causal relationship to study medication, occurring at any time for the duration of the study, from the time of signing the informed consent up to and including progression free follow-up and survival follow-up.

[redacted]

[redacted]

[redacted]



10. STUDY POPULATION

10.1. Subject Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Must understand and voluntarily sign an informed consent form.
2. Must be ≥18 years at the time of signing the informed consent form.
3. Must be able to adhere to the study visit schedule and other protocol requirements.
4. Must have a documented diagnosis of B-cell CLL (IWCLL guidelines for the diagnosis and treatment of chronic lymphocytic leukemia [redacted]).
5. Must have been treated with one of the following in first and/or second line:
   - a purine analog-containing regimen
   - a bendamustine-containing regimen
   - an anti-CD20 antibody-containing regimen
   - a chlorambucil-containing regimen
   - an alemtuzumab-containing regimen (for those subjects with a 17p deletion)
6. Must have achieved a minimum response of partial response (PR, nPR, CRi, CR, and MRD-negative CR) (IWCLL guidelines for the diagnosis and treatment of chronic lymphocytic leukemia [redacted] Appendix 22.4) following completion of second-line induction therapy prior to randomization (documentation of response status must be available). Second-line induction therapy must be documented to have been of sufficient duration.
7. Must have completed last cycle of second-line induction no less than 8 weeks (56 days) and no greater than 20 weeks (140 days) prior to randomization.
8. Must have an ECOG performance status score of ≤2.
9. Females of childbearing potential (FCBP)[†] must:
   - Have two negative medically supervised pregnancy tests prior to starting of study therapy. She must agree to ongoing pregnancy testing during the course of the study, and after end of study therapy. (see specifics in Appendix 22.6). This applies even if the subject practices complete and continued sexual abstinence.

[†] Definition found in appendices

- Either commit to continued abstinence from heterosexual contact (which must be reviewed on a monthly basis) or agree to use, and be able to comply with, effective contraception without interruption, 28 days prior to starting study drug, during the study therapy (including dose interruptions), and for 28 days after discontinuation of study therapy (see specifics in Appendix 22.6).

10. Male subjects must:
    - Commit to continued abstinence from heterosexual contact or agree to use a condom during sexual contact with a FCBP, even if they have had a vasectomy, throughout study drug therapy, during any dose interruption and after cessation of study therapy. (see specifics in Appendix 22.6)
    - Agree to not donate semen during study drug therapy and for a period after end of study drug therapy (see specifics in Appendix 22.6).
11. All subjects must:
    - Have an understanding that the study drug could have a potential teratogenic risk.
    - Agree to abstain from donating blood while taking study drug therapy and following discontinuation of study drug therapy. (See specifics in Appendix 22.6)
    - Agree not to share study medication with another person.
    - All subjects must be counseled about pregnancy precautions and risks of fetal exposure. See Appendix 22.6.

10.2. Subject Exclusion Criteria

1. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
2. Active infections requiring systemic antibiotics.
3. Systemic infection that has not resolved > 2 months prior to initiating lenalidomide treatment in spite of adequate anti-infective therapy
4. Autologous or allogeneic bone marrow transplant as second-line therapy.
5. Pregnant or lactating females.
6. Systemic treatment for B-cell CLL in the interval between completing the last cycle of second-line induction therapy and randomization.
7. Participation in any clinical study or having taken any investigational therapy for a disease other than CLL within 28 days prior to initiating maintenance therapy.
8. Known presence of alcohol and/or drug abuse.
9. Central nervous system involvement as documented by spinal fluid cytology or imaging. Subjects who have signs or symptoms suggestive of leukemic meningitis or a history of leukemic meningitis must have a lumbar puncture procedure performed within two weeks prior to randomization.

10. Prior history of malignancies, other than CLL, unless the subject has been free of the disease for ≥5 years. Exceptions include the following:
    - Basal cell carcinoma of the skin
    - Squamous cell carcinoma of the skin
    - Carcinoma *in situ* of the cervix
    - Carcinoma *in situ* of the breast
    - Incidental histologic finding of prostate cancer (tumor-nodes-metastasis [TNM] stage of T1a or T1b)
11. History of renal failure requiring dialysis.
12. Known Human Immunodeficiency Virus (HIV), active Hepatitis B Virus (HBV), and/or active Hepatitis C Virus (HCV) infection.
13. Prior therapy with lenalidomide.
14. Evidence of TLS per the Cairo-Bishop definition of laboratory TLS (Appendix 22.5) (subjects may be enrolled upon correction of electrolyte abnormalities).
15. Any of the following laboratory abnormalities:
    - Calculated (method of Cockroft-Gault) creatinine clearance <60 mL/min.
    - Absolute neutrophil count (ANC) <1,000/µL (1.0 X 10^9/L)
    - Platelet count <50,000/µL (50 X 10^9/L)
    - Serum aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) or alanine transaminase (ALT)/serum glutamate pyruvate transaminase (SGPT) > 3.0 x upper limit of normal (ULN)
    - Serum total bilirubin >2.0 mg/dL (with the exception of Gilbert's Syndrome)
16. Grade 4 rash due to prior thalidomide treatment
17. Uncontrolled hyperthyroidism or hypothyroidism
18. Venous thromboembolism within one year
19. ≥Grade-2 neuropathy
20. Uncontrolled autoimmune hemolytic anemia or thrombocytopenia
21. Disease transformation (active) (ie, Richter's Syndrome, prolymphocytic leukemia)
22. Known allergy to allopurinol for subjects assessed with PR following their second-line induction therapy.
23. Prisoners.
24. More than 2 prior lines of CLL therapy.

11. DESCRIPTION OF TREATMENT

11.1. Description of Study Drug

Celgene Corporation will supply lenalidomide 2.5 mg, 5 mg, and 10 mg capsules for oral administration. Subjects dose reduced to 7.5 mg dose level (as outlined in Section 10.2.1) will receive one 5.0 mg capsule and one 2.5 mg capsule daily.

Study drug will be packaged in bottles containing study capsules for 28 days. Subjects assigned to active treatment will receive 28 days of active drug (with the exception of those subjects de-escalated to 2.5 mg every other day).

Celgene Corporation will no longer supply blinded allopurinol 300 mg and matching placebo (Amendment #10).

Subjects currently on lenalidomide treatment will discontinue lenalidomide treatment immediately. Celgene Corporation will no longer supply lenalidomide (Amendment #11).

11.1.1. Randomization

Randomization will be accomplished by an IVRS to ensure timely registration and randomization. Designated research personnel at the investigational sites will be assigned password protected, coded identification numbers, which gives them authorization to call into the IVRS to enroll subjects. The system will present a menu of questions by which the research personnel will identify the subject and confirm eligibility. When all questions have been answered, including questions regarding the results of pregnancy tests for FCBP, the IVRS will assign a subject number and study drug to the eligible subject. IVRS will fax a confirmation of registration and drug assignment for each subject to the site and Celgene. Subjects will be randomized (1:1) to receive lenalidomide or placebo. Subjects will be stratified at randomization by: 1) their response to second-line induction therapy (PR, nPR, CRi or CR versus MRD-negative CR); 2) age (≤ 70 versus > 70 years); and 3) presence of at least one of the following poor prognostic factors: 11q deletion, 17p deletion, unmutated IgV_H, or β2M > 4.0 mg/L (Yes versus No versus Unknown).

Site staff are to contact Celgene at each visit for study drug assignment, to register dose reductions or escalations, and at discontinuation from treatment. Confirmation of each call will be faxed to the site.

11.2. Treatment Assignments

Lenalidomide

Oral lenalidomide 2.5 mg capsule once daily on Days 1 through 28 of the first 28-day cycle. If the 2.5 mg dose is well tolerated, subjects should be escalated starting at the second cycle to 5 mg capsule once daily on Days 1 through 28 of each 28-day cycle to disease progression [redacted]. If a subject develops a Grade 1 or 2 adverse event, the drug may be interrupted until resolution, however the subject must complete one full cycle at the 2.5 mg dose level prior to escalation to the 5 mg dose level.

Following 5 continuous cycles at the 5 mg dose level, subjects who are tolerating the 5 mg dose level may be escalated to 10.0 mg once daily on days 1 through 28 of each 28-day cycle up to disease progression [redacted]

Amendment #11:

Subjects currently on lenalidomide treatment will discontinue lenalidomide treatment immediately and complete the Treatment Discontinuation assessment. The subjects will then transition to the survival follow-up period.

11.2.1. Dose Modification or Interruption

Subjects will be evaluated for AEs at each visit with the NCI CTCAE (Version 3.0) used as a guide for the grading of severity with the exceptions recommended by the IWCLL guidelines for the diagnosis and treatment of chronic lymphocytic leukemia [redacted] as listed below*:

Table 4: Grading Scale for Hematological Toxicity in CLL Studies

Grade#	Decrease in Platelets* or Hb° (nadir) From Pretreatment value (%)	Absolute neutrophil count/µL@ (nadir)
0	No change to 10%	≥ 2,000
1	11% - 24%	≥1,500 and < 2,000
2	25% - 49%	≥1,000 and < 1,500
3	50% - 74%	≥ 500 and < 1,000
4	≥ 75%	< 500

* Platelet counts must be below normal levels for grades 1-4. If, at any level of decrease the platelet count is <20,000/µL, this will be considered grade 4 toxicity, unless a severe or life-threatening decrease in the initial platelet count (eg, 20,000/µL) was present pretreatment, in which case the patient is not evaluable for toxicity referable to platelet counts.

° Hb levels must be below normal levels for grades 1-4. Baseline and subsequent Hb determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity, but should be documented.

Grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, fatal. Death occurring as a result of toxicity at any level of decrease from pretreatment will be recorded as grade 5.

@ If the absolute neutrophil count (ANC) reaches less than 1,000/µL, it should be judged to be grade 3 toxicity. Other decreases in the white blood cell count, or in circulating granulocytes, are not to be considered, since a decrease in the white blood cell count is a desired therapeutic end point. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. The use of G-CSF is irrelevant for the grading toxicity, but should be documented.

In addition, TLS will be graded as specified by the Cairo-Bishop grading system (Appendix 22.5). Subjects meeting criteria of laboratory TLS or ≥ Grade 1 TLS, will be hospitalized (per investigator's discretion for laboratory TLS), provided with vigorous intravenous hydration and appropriate therapy (ie, rasburicase where available) as needed to reduce hyperuricemia, until correction of electrolyte abnormalities. In the case of laboratory TLS and Grade 1 TLS, lenalidomide will be continued at the same dose without interruption or dose reduction. Subjects with ≥ Grade 2 TLS, will have their dose interrupted and will resume lenalidomide at the next lower dose level when electrolyte abnormalities are corrected (ie, Grade 0). If lenalidomide is

resumed prior to the start of the subsequent cycle, chemistry tests should be performed every other day for the first week following initiation of lenalidomide.

If a subject develops toxicity (Table 6), the dose may be reduced as outlined in Table 5.

Table 5: Dose Reduction Steps

Lenalidomide Dose	2.5 mg every day x 28 days of a 28-day cycle	5 mg every day x 28 days of a 28-day cycle	10 mg every day x 28 days of a 28-day cycle
Dose Reduction – 1	2.5 mg every other day x 28 days of a 28-day cycle	2.5 mg every day x 28 days of a 28-day cycle	7.5 mg every day x 28 days of a 28- day cycle
Dose Reduction – 2	n/a	2.5 mg every other day x 28 days of a 28-day cycle	5 mg every day x 28 days of a 28- day cycle
Dose Reduction – 3	n/a	n/a	2.5 mg every day x 28 days of a 28- day cycle
Dose Reduction – 4	n/a	n/a	2.5 mg every other day x 28 days of a 28-day cycle

Subjects experiencing a ≥ Grade 3 non-hematologic AE will have their study drug held until resolution of the AE as described in Table 6: Dose Reduction and Modification Guidelines. Subjects with a hematologic AE will modify study drug dosing as outlined in Table 6.

Subjects who cannot tolerate 2.5 mg every other day x 28 days of a 28-day cycle are to be discontinued from study drug and followed for survival as outlined in Table 2.

Table 6: Dose Reduction and Modification Guidelines

NCI CTCAE Toxicity Grade	Action
Neutropenia ANC < 400/uL	• Interrupt study drug therapy • Resume study drug (decrease one dose level) when ANC recovers to ≥ 500/uL
Thrombocytopenia < 20,000/uL	• Interrupt study drug therapy • Resume study drug (decrease one dose level) when platelet count recovers to ≥ 25,000/uL
Syndromes	
Tumor Flare Grade 3 or 4	• Interrupt study drug therapy and initiate therapy with NSAIDs, narcotic analgesics or prednisone • Resume study drug (decrease one dose level) when symptoms resolve to ≤ Grade 2
Desquamating (blistering) rash	• Discontinue study drug
Non- desquamating rash Grade 3	• Interrupt study drug therapy.

NCI CTCAE Toxicity Grade	Action
Grade 4	• Resume study drug when the rash resolves to ≤ Grade 1 (decrease one dose level) • Discontinue study drug

Table 6: Dose Reduction and Modification Guidelines (Continued)

NCI CTCAE Toxicity Grade	Action
Neuropathy Grade 3 Grade 4	 • If Grade 3, interrupt study drug therapy. • Resume study drug when the neuropathy resolves to ≤ Grade 1 (decrease one dose level) • If Grade 4, discontinue study drug
Venous thrombosis/embolism ≥ Grade 3	• Hold (interrupt) dose and start anticoagulation; • Resume study drug when adequately anticoagulated (maintain dose level).
Hyperthyroidism or hypothyroidism	• Interrupt study drug and initiate appropriate medical therapy. • Resume study drug when appropriately controlled (maintain dose level).
Serum Creatinine Grade 1 **It is possible for subjects entering the study with a creatinine clearance ≥ 60 ml/min and a serum creatinine at the upper limit of normal to show slight fluctuations of the serum creatinine above the upper limit of normal. It is left at the investigator's discretion to measure the creatinine clearance for those subjects to evaluate whether a dose adjustment is needed.	 • Interrupt study drug • Evaluate subject weekly x 3 weeks • If during those 3 weeks, the creatinine level worsened at any time to > Grade 1, permanently discontinue and follow for PD • If at the end of the third week the creatinine level has improved to < Grade 1, resume study drug (maintain dose level) • If at the end of the third week the creatinine level has stabilized at Grade 1, resume study drug (decrease one dose level) • Following resumption of study drug, evaluate subject weekly x 2 weeks to ensure creatinine level does not worsen; if creatinine level again worsens during those 2 weeks, permanently discontinue and follow for PD
Grade 2	• Interrupt study drug • Evaluate subject weekly x 3 weeks • If during those 3 weeks, the creatinine level worsened at any time to > Grade 2, permanently discontinue and follow for PD

NCI CTCAE Toxicity Grade	Action
	• If at the end of the third week, the creatinine level has improved to < Grade 1 resume study drug (maintain dose level) • If at the end of the third week, the creatinine level has improved to a Grade 1 or has stabilized at Grade 2, resume study drug (decrease one dose level)

Table 6: Dose Reduction and Modification Guidelines (Continued)

NCI CTCAE Toxicity Grade	Action
	• Upon resumption of study drug, evaluate subject weekly x 2 weeks to ensure creatinine level does not worsen; if creatinine level again worsens during those 2 weeks, permanently discontinue and follow for PD
Grade 3	• Interrupt study drug • Evaluate subject weekly x 3 weeks • If during those 3 weeks, the creatinine level worsened at any time to > Grade 3, or if dialysis is indicated, permanently discontinue and follow for PD • If at the end of the third week, the creatinine level has improved to ≤ Grade 2 resume study drug (decrease one dose level) • Upon resumption of study drug, evaluate subject weekly x 2 weeks to ensure creatinine level does not worsen; if creatinine level again worsens during those 2 weeks, permanently discontinue and follow for PD • If at the end of the third week, the creatinine level has not improved to < Grade 3, permanently discontinue and follow for PD
Grade 4 OR if dialysis is indicated	• Permanently discontinue and follow for PD
Cairo-Bishop Toxicity Grade	
Clinical TLS ≥ Grade 2	• Interrupt lenalidomide therapy. • May resume lenalidomide when the TLS resolves to < Grade 1 (decrease one dose level)

Table 6: Dose Reduction and Modification Guidelines (Continued)

NCI CTCAE Toxicity Grade	**Action**	
Chemistry value	**Action**	**Lenalidomide Dose Modification**
• ALT > 3.0 and ≤ 5.0 x ULN AND • Serum total bilirubin ≤ 2.0 mg/dL (~1.5 x ULN)	• Continue current dose level • Test at next scheduled visit	• None Required – continue current dose level.
• ALT > 3.0 and ≤ 5.0 x ULN **AND** • Serum total bilirubin > 2.0 mg/dL (~1.5 x ULN)	• Temporarily Discontinue lenalidomide • Re-test weekly until ALT and total bilirubin return to baseline	• Resume the same dose of lenalidomide if recovery from the event is ≤ 14 days. • If recovery occurs > 14 days but ≤ 28 days, the lenalidomide dose should be decreased by one dose level, and weekly testing of liver functions should occur during that cycle. • If the event does not repeat, dose escalation or re-escalation may continue according to the protocol. • If the values do not return to baseline within 28 days, the medical monitor must be notified.
• ALT >5.0 x ULN **AND/OR** • Serum total bilirubin > 2.0 mg/dL (~1.5 x ULN)	• Temporarily Discontinue lenalidomide • Re-test weekly until ALT and total bilirubin return to baseline	• Resume the same dose of lenalidomide if recovery from the event is ≤ 14 days. • If recovery occurs > 14 days but ≤ 28 days, the lenalidomide dose should be decreased by one dose level, and weekly testing of liver functions should occur during that cycle. • If the event does not repeat, dose escalation or re-escalation may continue according to the protocol. • If the values do not return to baseline within 28 days, the medical monitor must be notified.

Table 6: Dose Reduction and Modification Guidelines (Continued)

NCI CTCAE Toxicity Grade	Action	
Other lenalidomide-related non-hematologic AEs	≥ Grade 3	• Interrupt lenalidomide therapy. • May resume lenalidomide when the adverse event resolves to ≤ Grade 2 (decrease one dose level or maintain dose level per the investigator's discretion)

A new course of treatment may begin on the scheduled Day 1 of a new cycle if:

- the ANC is ≥ 500/μL;
- the platelet count is ≥ 25,000/μL;
- any other lenalidomide-related non-hematologic adverse event that may have occurred has resolved as indicated in Table 6.

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly and a new cycle will not be initiated until the toxicity has resolved as described above.

Dose interruptions/reductions are permitted for Grade 1 or 2 adverse events at the investigator's discretion.

If a study drug interruption has lasted for 5 weeks, the investigator should contact the medical monitor to discuss whether the subject should be continued on the study.

Site staff are to contact Celgene to record new dose level and obtain new study drug assignment. If the treatment has been withheld and the next treatment cycle is delayed beyond 29 days after Day 1 of the prior treatment cycle, then Day 1 of the next treatment cycle will be defined as the first day that the treatment is resumed. If dose reduction occurs within a cycle, subjects will be given a new 28-day supply bottle, subjects should begin taking study drug at the current cycle day (ie, if reduction occurs on Cycle Day 16, then the subject will take study drug from the new bottle for the remainder of the cycle). Subjects will be required to return empty bottle or any unused drug prior to new drug being dispensed.

Dose re-escalation is permitted if the subject is able to complete 2 full cycles at the reduced dose level without experiencing a DLT or other toxicity deemed to be unacceptable by the investigator or subject. In the event the dose reduction is implemented due to Grade 4 neutropenia, subjects may be re-escalated after one full cycle at the lower dose level if the neutropenia resolves to a Grade 2 or better by the end of the cycle and no other DLT is observed. If that dose level is again not tolerated, the subject should be de-escalated to the dose below and remain at that tolerated dose level for the rest of the study.

Allopurinol Dose Adjustment Guidelines:

Allopurinol should be permanently discontinued for any adverse reaction deemed possibly related to allopurinol administration.

For a Grade 1 or 2 rash, allopurinol should be discontinued prior to study drug to try to determine causality. If the rash does not improve, the study drug should be adjusted per the investigator's discretion.

For a Grade 3 or 4 rash, allopurinol should be discontinued and study drug adjusted as outlined in Table 6.

In the event of development of renal impairment, allopurinol should be discontinued and study drug adjusted as outlined in Table 6.

For all other AEs, study drug should be adjusted as outlined above.

11.3. Blinding

This is now an open-label protocol. Therefore the dose of study drug will be identified on the package labeling (Amendment #10).

11.4. Emergency Unblinding

This is now an open-label protocol. Therefore the dose of study drug will be identified on the package labeling (Amendment #10).

[redacted]

11.6. Discontinuation from Treatment

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

- AEs that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of study drug.
- Disease progression with or without histologic transformation
- Subject withdraws consent

- Subject lost to follow-up
- Death
- Protocol violation

The reason for discontinuation should be recorded in the CRF and in the subject's medical records. Celgene is to be notified of all discontinuations from study drug.

12. EMERGENCY PROCEDURES

12.1. 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 and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on call Celgene/CRO 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. STUDY DRUG MATERIALS AND MANAGEMENT

13.1. Supplier(s)

Celgene Corporation will supply lenalidomide capsules.

Celgene Corporation will no longer supply blinded allopurinol and matching placebo (Amendment #10).

Celgene Corporation will no longer supply lenalidomide (Amendment #11).

13.2. Dosage Form

Lenalidomide will be supplied as 2.5 mg, 5 mg, and 10 mg capsules for oral administration. Subjects dose reduced to 7.5 mg dose level (as outlined in Section 10.2.1) will receive one 5.0 mg capsule and one 2.5 mg capsule daily.

13.3. Dosage Regimen

Subjects will be randomized (1:1) via IVRS to receive the following:

- Oral lenalidomide 2.5 mg capsule once daily on days 1-28 of the first 28 day cycle and if tolerated should be escalated starting with the second cycle to a 5 mg capsule once daily on days 1-28 of a 28 day cycle up to disease progression ~~or October 2020, whichever comes first~~.

  Following 5 continuous cycles at the 5 mg dose level, subjects who are tolerating the 5 mg dose level may be escalated to 10 mg once daily on days 1 through 28 of each 28-day cycle up to disease progression ~~or October 2020, whichever comes first~~.

- Oral placebo capsule once daily every day for a 28 day cycle up to disease progression. The placebo treatment arm is discontinued in amendment #10.

Amendment #11:

Subjects currently on lenalidomide treatment will discontinue lenalidomide treatment immediately and complete the Treatment Discontinuation assessment. The subjects will then transition to the survival follow-up period.

13.4. Study Drug Packaging and Labeling

Celgene Corporation will supply lenalidomide 2.5 mg, 5 mg, and 10 mg capsules for oral administration. Subjects dose reduced to 7.5 mg dose level (as outlined in Section 10.2.1) will receive one 5.0 mg capsule and one 2.5 mg capsule daily.

The lenalidomide study drug will be packaged in 28-count bottles.

The label for study drug supplied by Celgene will bear Celgene's name and address, the protocol number, EudraCT number (where required), product name, dosage form, and strength, medication identification/kit number, dosing instructions, storage conditions, the quantity of study drug contained, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as needed and/or applicable

Subjects requiring dose reduction within a treatment cycle must return to the study site and return the empty bottles or any unused drug and a new bottle will be dispensed. Subjects will be given a new 28-day supply bottle and should begin taking study drug at the current cycle day.

13.5. Study Drug Receipt and Storage

The Investigator(s) is responsible for taking an inventory of each shipment of study drug received, and comparing it with the accompanying study drug shipping order form. The Investigator(s) will verify the accuracy of the information on the form and call Celgene to register the study medication received at the site.

At the study site, all investigational study drugs will be stored in a locked, safe area to prevent unauthorized access.

The study drug should be stored as directed on package label.

13.6. Record of Administration

Accurate recording of all study drug administration (including dispensing and dosing) will be made in the appropriate section of the subject's CRF and source documents.

13.7. Study Drug Accountability

The Investigator(s) or designee(s) is responsible for accounting for all study drug that is issued to and returned by the subject during the course of the study.

13.8. Study Drug Handling and Disposal

FCBP should not handle or administer study drug unless they are wearing gloves. All patients should not extensively handle or open study drug capsules and should maintain storage of capsules in the packaging until ingestion.

In investigational studies, study drug 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 patients. Once trained these healthcare staff will counsel patients prior to study drug being dispensed to ensure that the patient has complied with all requirements including use of birth control and pregnancy testing (FCBP) and that the patient understands the risks associated with lenalidomide. This step will be documented with a completed lenalidomide Education and Counseling Guidance Document (Appendix 22.6), and no drug will be dispensed until this step occurs. Counseling includes verification with the patient that required pregnancy testing was performed and results were negative. A Lenalidomide Information Sheet (Appendix 22.6) will be supplied with each study drug dispense.

Celgene will instruct the Investigator(s) on the return or destruction of unused study drug. If any study drug is lost or damaged, its disposition should be documented in the subject's CRF and source documents. Celgene will provide instructions for the return of study drug supplies at the end of the study.

14. ASSESSMENT OF EFFICACY

14.1. Assessments

- Survival/Date of death

14.2. Methods and Timing of Efficacy Assessments

Serial measurements of efficacy will be performed at baseline and at scheduled intervals throughout the duration of the study as outlined in Table 2. All scheduled visits will have a ± 3 day window unless otherwise stated.

15. ASSESSMENT OF SAFETY

15.1. Assessments

- Clinical laboratory evaluations:
  - Hematology: white blood cell (WBC), hemoglobin (HGB), hematocrit (HCT), platelet count, absolute neutrophil count (ANC), and absolute lymphocyte count (ALC)
  - Chemistry: calculated (method of Cockroft-Gault) creatinine clearance (screening only), potassium, calcium, phosphorus, creatinine, alkaline phosphatase, total bilirubin, AST/SGOT, ALT/SGPT, and uric acid
- Pregnancy testing for FCBP: serum or urine beta-human chorionic gonadotropin hormone (β-HCG) pregnancy testing with a sensitivity of at least 25 mIU/mL is to be done on FCBP only
  - FCBP should be monitored during the course of the study and after the end of study therapy to:
    - Ensure that pregnancy tests are performed during the course of the study and after end of study therapy and are negative (see specifics in Appendix 22.6).
    - Ensure the patient continues to practice abstinence or remains on adequate contraception (see specifics in Appendix 22.6).
    - If a FCBP becomes pregnant treatment should be stopped and the patient referred to the appropriate physician
- Male patients should be monitored during the course of the study and 28 days after the end of study therapy to:
  - Ensure they commit to continued abstinence from heterosexual contact or continue to use a condom during sexual contact with a FCBP
  - If a female partner of a male patient becomes pregnant she should be referred to an appropriate physician
- Concomitant medications
- AEs by NCI CTCAE Version 3.0 with modifications recommended by the IWCLL guidelines for the diagnosis and treatment of chronic lymphocytic leukemia [redacted]
- Second primary malignancies will be monitored as events of interest and should be included as part of the assessment of adverse events throughout the course of the study. Investigators are to report any second primary malignancies as serious adverse events regardless of causal relationship to study drug, occurring at any time for the duration of the study, from the time of signing the informed consent up to and including the survival follow up phase.

15.2. Methods and Timing of Safety Assessments

Serial measurements of safety will be performed at baseline and at scheduled intervals throughout the duration of the study as outlined in Table 2. All scheduled visits will have a ± 3 day window unless otherwise stated. Abnormalities will be captured as adverse events. The adverse event of flare reaction, which may mimic disease progression, may render the efficacy assessments not evaluable at the corresponding visit(s). Cause of death is to be recorded in the CRF and the subject's medical record.

15.3. Recording and Reporting of Adverse Events

The recording and reporting of adverse events is described in Appendix 22.1.

[redacted]

17. STATISTICAL ANALYSES

17.1. Statistical Overview

The objective of the statistical analysis will be to compare the efficacy and safety of lenalidomide versus placebo as maintenance therapy in subjects with relapsed or refractory B-cell chronic lymphocytic leukemia (CLL) having achieved PR or better after second-line therapy.

Overall survival (OS) will be the primary endpoint for the protocol following amendment #10. This analysis will be performed at the completion of the study. It is estimated that at least 160 subjects across both treatment arms have died at the time of analysis (yielding 80% power to detect a 61.3% improvement in median OS for a two-sided test at 0.025 level allowing for one interim analysis).

17.2. Study Population Definitions

17.2.1. Intent-to-Treat Population

The primary efficacy analysis will be performed on the intent-to-treat (ITT) population, which will include all subjects who were randomized.

17.2.2. Safety Population

All randomized subjects who receive any study drug will be included in the safety analyses.

17.2.3. Subgroup Analyses

In addition to analyses that include all subjects, analyses will be performed to compare treatments within the following stratification subgroups:

- Response to second-line induction chemotherapy (PR, CRi or CR versus MRD-negative CR)
- Age (≤ 70 years versus > 70 years)
- Presence of at least one of the following poor prognostic factors: 11q deletion, 17p deletion, unmutated IgV_H or β2M > 4.0 mg/L (Yes versus No versus Unknown)

Additional subgroups may be examined, as needed based on regulatory and clinical requests.

17.3. Efficacy Evaluation

17.3.1. Primary Endpoint

Overall Survival (OS)

Overall survival is calculated as the time from randomization to death from any cause. OS will be censored at the last date that the subject was known to be alive for subjects who were alive at the time of analysis and for subjects who were lost to follow-up before death was documented.

The analysis of OS will include survival information for all randomized subjects. Subjects who discontinued from the treatment phase of the study and who had possibly received other anti-cancer therapies and then subsequently died will be included in the analysis as death. However, sensitivity analyses will be performed in which these subjects will be censored at the date of the first dose date of the anti-cancer therapy.

17.3.2. Secondary Endpoint

Progression Free Survival 2 (PFS2)

PFS is defines as the time from randomization to the second objective disease progression, or death from any cause, whichever occurs first. Patients alive and for whom a second objective disease progression has not been observed should be censored at the last time known to be alive and without second objective disease progression. In situations where OS and PFS2 cannot reliably be determined, it may be possible to rule out significant lack of efficacy of further treatments by looking at the outcome of the next line therapy. For this analysis, an event is defined as second objective disease progression, or death from any cause, or the start of the CLL therapy after next line treatment, whichever occurred first (EMEA guideline 13 DEC 2012). Various schemes will be assessed for missing data imputation if needed.

17.3.3. Efficacy Analyses

Kaplan-Meier product limit methods will be used to estimate the survivorship functions for the time-to-event endpoints (eg, OS, and PFS2). A two-sided log-rank test stratified by the 3 strata used in the randomization will be used as the primary analytic method to compare survivorship functions for time-to-event variables in the 2 treatment groups. In terms of the survivorship functions for each treatment group, the hypotheses of interest were:

H_0: $F_A(t) = F_P(t)$ for all t

Versus

H_1: $F_P(t) \neq F_A(t)$ for all t

where F_P is the survivorship function for placebo and F_A is the survivorship function for lenalidomide.

Median OS will be estimated using Kaplan-Meier estimates, and the 95% confidence intervals (CI) will be computed using the method of Brookmeyer and Crowley. Hazard ratio will be calculated using Cox model stratified for the 3 strata (ie, response to second-line induction chemotherapy, age, and presence of at least one prognostic factor) to account for the stratified randomization. The Cox model will also be used to identify prognostic factors.

Cross-tabulations will be provided by treatment group to summarize improvements from the best response during induction therapy.

17.4. Background and Demographic Characteristics

Subjects' age, weight, height, and other continuous demographic and baseline variables will be summarized using descriptive statistics (mean, standard deviation, minimum, and maximum), while performance status, gender, race, and other categorical variables will be summarized with frequency tabulations for each treatment group separately and pooled over both treatment

regimens. Medical history data will be summarized using frequency tabulations for each treatment arm separately and pooled over both arms. Individual subject listings will be provided.

Homogeneity of these variables will be assessed by one-way analysis of variance for continuous measures and Fisher's exact test for categorical measures.

17.5. Study Drug

Dosage statistics (mean, median, mode, standard deviation and final dose, dose at each evaluation) will be provided. Reasons for discontinuation will be summarized.

[redacted]

17.7. Safety Evaluation

All subjects who receive at least one dose of study medication will be included in the safety analyses.

Adverse events (AE) will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. The severity of the toxicities will be graded according to the NCI CTCAE version 3.0 whenever possible.

The adverse event of infection will also be analyzed according to the grading system as recommended by the IWCLL guidelines for the diagnosis and treatment of CLL [redacted] (Appendix 22.4).

AE frequency will be tabulated by body system, MedDRA preferred term for each treatment regimen during the Treatment Phase. In the by-subject analysis, a subject having the same event more than once will be counted only once. AEs will be summarized by worst NCI CTCAE version 3.0 grade. AEs leading to death or to discontinuation from treatment, events classified as NCI CTCAE version 3.0 Grade 3 or higher, study-drug-related events, serious adverse events (SAEs), and events of interest (including second primary malignancies) will be summarized separately.

Laboratory data will be graded according to NCI CTCAE version 3.0 severity grade. Cross tabulations will be provided to summarize frequencies of abnormalities.

For vital sign and body weight data, means, medians, standard deviations, minimum, and maximum values will be provided.

Graphical displays will be provided where useful to assist in the interpretation of results.

[redacted]

17.9. Sample Size and Power Considerations

For OS, a 61.3% improvement in median survival from randomization, from 3 years for placebo to 4.83 years on lenalidomide is considered clinically relevant. The OS is assumed to be exponential with a constant failure (hazard) rate. When the total number of events is approximately 160 over both treatment arms, then a two-sided log-rank test with an overall significance level of 0.025 (allowing for one interim analysis) would have 80% power to detect a hazard rate ratio of 0.62 (that is, if the survival curves are exponential, to detect a 61.3% difference in the median OS in the 2 arms). To ensure timely completion of the study, 320 subjects will be enrolled, 160 in each treatment arm. Enrollment will close once 320 subjects are randomized or 160 adjudicated PFS events are reached, whichever comes first.

18. QUALITY CONTROL AND QUALITY ASSURANCE

18.1. Monitoring

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. Before the study is initiated at a site visit or at an investigator meeting, all aspects of the study are reviewed with the investigator(s) and the staff. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, CRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs with the Investigator(s). Monitoring will include on-site visits with the Investigator(s) and his/her staff as well as any appropriate communications by mail, fax, or telephone. At each monitoring visit, the facilities, study drug storage area, CRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative for adherence to the protocol and Good Clinical Practice.

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

18.2. Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene. From time to time, representatives of this unit will conduct audits of clinical research activities in accordance with Celgene standard operating procedures (SOPs) to evaluate compliance with Good Clinical Practice guidelines and regulations.

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

18.3. Investigator(s) Responsibilities

Investigator responsibilities are set out in the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice and in the US Code of Federal Regulations. Celgene or a representative will contact and select all principal investigators or co-investigators who in turn will select their staff. The investigator must give the monitor access to relevant records to confirm the above.

The Investigator(s) is responsible for keeping a record of all subjects who sign an Informed Consent Form and are screened for entry into the study. For those subjects who fail screening, the reason(s) for exclusion must be recorded in the subject's source documents and in the IVRS system.

No procedure/assessment/measurement/test other than those outlined here, or in the schedule of study assessments, is to be performed without the prior written approval of Celgene, or unless deemed by the investigator(s) as necessary for the subject's medical care. Investigator(s) and/or authorized designee(s) must enter study data onto CRFs supplied by Celgene. The data on the CRF will be recorded in an anonymous manner to protect the subject's identity by using a unique identifier that will prevent personal identifiable information.

The Investigator(s), or a designated member of the Investigators' staff, must be available at some time during monitoring visits to review data and resolve any queries and to allow direct access to the subject's records (eg, medical records, office charts, hospital charts, and study related charts) for source data verification. The CRFs must be completed as soon as possible after the subject's visit but no later than prior to each monitoring visit and be made available to the Celgene representative(s) so that the accuracy and completeness may be checked.

19. REGULATORY CONSIDERATIONS

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

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki (Appendix 22.2). The review of this protocol by the IRB/IEC and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Patients and Part 56 Institutional Review Boards. Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC). A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to Celgene before the study initiation. The names and occupations of the chairman and the members of the IRB/IEC must be supplied to Celgene.

The Investigator(s) will be responsible for preparing documents for submission to the relevant IRB/IEC and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study.

A copy of the IRB/IEC approval for the protocol and the Informed Consent is to be provided to Celgene. The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number.

The Investigator(s) is responsible for notifying the IRB/IEC of any serious deviations from the protocol, or anything else that may involve added risk to subjects.

Any advertisements used to recruit subjects for the study must be reviewed and approved by Celgene and the IRB/IEC prior to use.

19.2. Protocol Amendments

Any amendment to this protocol that seems appropriate, as the study progresses (eg, affects safety or efficacy) will be agreed upon between the coordinating and/or principal investigator(s) and the Celgene study physician. Amendments will be submitted to the IRB/IEC for written approval before the implementation of the amended version. The written signed approval from the IRB/IEC should refer specifically to the investigator(s) and to the protocol number and title and mention any amendment numbers that are applicable. Celgene does not require that amendments that are administrative in nature receive IRB/IEC approval, but will be submitted to the IRB/IEC for information purposes. If local IRB/IEC procedures require approval of administrative amendments, then study sites should follow local IRB/IEC regulations.

19.3. Informed Consent

The Investigator(s) must obtain informed consent of a subject or his/her designee prior to any study related procedures as per Good Clinical Practices (GCP) as set forth in the 21 CFR Parts 50 and 56 and ICH guidelines.

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

19.4. Patient Confidentiality

Celgene affirms the patient's right to protection against invasion of privacy. In compliance with United States federal regulations, Celgene requires the Investigator(s) to permit Celgene's representatives and, when necessary, representatives of the FDA or other 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 patient's statement of informed consent, it is the responsibility of the Investigator(s) to obtain such permission in writing from the appropriate individual.

20. DATA HANDLING AND RECORDKEEPING

20.1. Data/Documents

The investigator(s) must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug, CRFs, source documents, original documents, data, records (eg, hospital records; clinical and office charts; laboratory notes; memoranda; patient's diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; patient files), and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study are complete, accurate, filed and retained.

20.2. Data Management

Data will be entered into the clinical database as per Celgene SOPs. These data will be electronically verified through use of on-line checks during data entry, and through 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, in the form of a Data Clarification Form (DCF). Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data. A quality control audit will be performed per Celgene SOP(s).

20.3. Retention of Records

The investigator(s) must maintain records of all study documents and supporting information relating to the conduct of the study. This documentation includes, but is not limited to, protocols, case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with health authorities and IRBs/IECs, informed consent forms, investigator(s) curricula vitae, monitoring visit logs, laboratory reference ranges, laboratory certification or quality control procedures, and laboratory director curriculum vitae. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice specified below. The study monitor must be consulted if the investigator(s) wishes to assign the study files to someone else, remove them to another location or is unable to retain them for a specified period.

For studies conducted in the United States under a US Investigational New Drug (IND), the investigator(s) must retain the study records for a minimum of 2 years after a marketing application for the indication is approved or for 2 years after the IND is withdrawn. If no application is filed, or if the application is not approved for the indication, the records are to be retained for two years after the investigation (ie, the IND) is discontinued, and FDA is notified of that fact. For IND studies conducted outside the US, the investigator(s), must retain study records for the time period described above or according to local laws or requirements, whichever is longer. The monitor will inform the investigator(s) of the dates for retention. All study documents should be made available if required by relevant health authorities. For studies not conducted under the US IND, the investigator(s) records must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no

pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by other applicable regulatory requirements.

21. PREMATURE DISCONTINUATION OF THE STUDY

21.1. Single Site

The responsible clinical Investigator as well as Celgene have the right to discontinue a single site at any time during the study for reasonable medical or administrative reasons. Possible reasons for termination of the study could be, but are not limited to:

- Unsatisfactory enrollment with respect to quantity or quality
- Inaccurate or incomplete data collection
- Falsification of records
- Failure to adhere to the study protocol

21.2. Study as a Whole

Celgene reserves the right to terminate this clinical study at any time for reasonable medical or administrative reasons.

Any possible premature discontinuation would have to be documented adequately with reasons being stated, and information would be issued according to local requirements (eg, IRB/IEC, regulatory authorities, etc.).

[redacted]

[redacted]

[redacted]

[redacted]

23. APPENDICES

23.1. Adverse Event

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence occurring at any dose 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 medical condition that was present prior to study treatment and that remains unchanged or improved should not be recorded as an AE. If there is a worsening of that medical condition, this should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the electronic Case Report Form rather than the individual signs or symptoms of the diagnosis or syndrome.

All AEs will be recorded by the Investigator(s) from the time of signing of informed consent form to 30 days after the treatment discontinuation visit. All AEs that lead to study discontinuation should be followed until resolution or stabilization. AEs will be recorded on the AE page of the CRF and in the subject's source documents.

Abnormal laboratory values defined as adverse events

An abnormal laboratory value is considered to be an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study.
- Requires treatment, modification/interruption of study drug dose, or any other therapeutic intervention.
- Is judged by the Investigator(s) to be of significant clinical importance.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE.

Please note that all ≥ Grade 3 hematologic lab abnormalities must be reported as an Adverse Event on the AE page of the CRF.

Serious adverse event

A serious adverse event (SAE) is any AE which:

- Results in death
- Is life-threatening (ie, in the opinion of the Investigator[s] the subject is at immediate risk of death from the AE)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- 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 serious adverse events. This includes any second primary malignancy, regardless of causal relationship to study medication, occurring at any time for the duration of the study, from the time of signing the ICF up to and including any follow-up, observation and/or survival follow-up period. In this study, subjects will be followed until all subjects in the study have been followed for at least 5 years from the last randomization, October 2020 (or have died/become lost to follow-up before 5 years). Events of second primary malignancy 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 of the diagnosis of the second primary malignancy must be provided at the time of reporting as a serious adverse event (eg, any confirmatory histology or cytology results).

Events not considered to be SAEs are hospitalizations which: were planned before entry into the clinical study; are for elective treatment of a condition unrelated to the studied indication or its treatment; occur on an emergency outpatient basis and do not result in admission (unless fulfilling other criteria above); are part of the normal treatment or monitoring of the studied indication and are not associated with any deterioration in condition.

If an AE is considered serious, both the AE pages of the CRF and the SAE Report Form must be completed.

For each SAE, the Investigator(s) will provide information on severity, start and stop dates, relationship to study drug, action taken regarding study drug, and outcome.

Classification of severity

For both AEs and SAEs, the investigator(s) must assess the severity of the event.

The severity of AEs will be graded based upon the subject's symptoms according to National Cancer Institute (NCI) Common Terminology Criteria (CTCAE, Version 3.0) with the exceptions recommended by the IWCLL guidelines for the diagnosis and treatment of chronic lymphocytic leukemia [redacted] AEs will be evaluated for severity according to the following scale:

Grade 1 = Mild

Grade 2 = Moderate

Grade 3 = Severe

Grade 4 = Life Threatening or disabling AE

Grade 5 = Death

The following exceptions will be made as recommended by the IWCLL guidelines for the diagnosis and treatment of chronic lymphocytic leukemia [redacted] as listed below*:

Grade#	Decrease in Platelets* or Hb° (nadir) From Pretreatment value (%)	Absolute neutrophil count/µL@ (nadir)
0	No change to 10%	≥ 2,000
1	11% - 24%	≥1,500 and < 2,000
2	25% - 49%	≥1,000 and < 1,500
3	50% - 74%	≥ 500 and < 1,000
4	≥ 75%	< 500

* Platelet counts must be below normal levels for grades 1-4. If, at any level of decrease the platelet count is < 20,000/µL, this will be considered grade 4 toxicity, unless a severe or life-threatening decrease in the initial platelet count (eg, 20,000/µL) was present pretreatment, in which case the patient is not evaluable for toxicity referable to platelet counts.

° Hb levels must be below normal levels for grades 1-4. Baseline and subsequent Hb determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity, but should be documented.

Grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, fatal. Death occurring as a result of toxicity at any level of decrease from pretreatment will be recorded as grade 5.

@ If the absolute neutrophil count (ANC) reaches less than 1,000/µL, it should be judged to be grade 3 toxicity. Other decreases in the white blood cell count, or in circulating granulocytes, are not to be considered, since a decrease in the white blood cell count is a desired therapeutic end point. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was less than 1,000/µL prior to therapy, the patient is not evaluable for toxicity referable to the ANC. The use of G-CSF is irrelevant for the grading toxicity, but should be documented.

Grade 4 hematologic abnormalities are expected in patients with CLL, and are also observed in patients receiving lenalidomide. During the conduct of CC-5013-CLL-002, all Grade 4 laboratory abnormalities will be reported to Celgene Drug Safety as SAEs at the discretion of the investigator and recorded in the CRF as SAEs, however those that are not deemed by the investigator to be part of a diagnosis or syndrome will not reported to the Health Authorities in an expedited manner. Laboratory values will be captured within the study database and will be reviewed on an ongoing basis by the sponsor and (provided that it is determined that any observed individual abnormalities or patterns of abnormalities do not warrant prompt communication to Health Authorities) will be reported to Health Authorities in periodic safety reports.

Please note that all ≥ Grade 3 hematologic lab abnormalities must be reported as an Adverse Event on the AE page of the CRF.

Classification of Relationship/Causality of adverse events (SAE/AE) to study drug

The Investigator(s) must determine the relationship between the administration of study drug and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected: The temporal relationship of the adverse event to study drug administration makes **a causal relationship unlikely or remote**, or other medications, therapeutic interventions, or

underlying conditions provide a sufficient explanation for the observed event

Suspected: The temporal relationship of the adverse event to study drug administration makes **a causal relationship possible,** and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

Monitoring and reporting of adverse events

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.

Immediate reporting of serious adverse events

Any AE that meets the criterion for a SAE requires the completion of a SAE Report Form in addition to being recorded on the AE pages of the CRF. The Investigator(s) is required to ensure that the data on these forms is accurate and consistent. This applies to all SAEs, regardless of relationship to study drug, that occur during the study, those made known to the Investigator(s) within 30 days after a subject's treatment discontinuation visit, and those made known to the investigator(s) at anytime that are suspected of being related to study drug.

Second primary malignancies will be monitored as events of interest and must be reported as serious adverse events. This includes any second primary malignancy, regardless of causal relationship to study medication, occurring at any time for the duration of the study, from the time of signing the ICF up to and including any follow-up, observation and/or survival follow-up period. In this study, subjects will be followed until all subjects in the study have been followed for at least 5 years from the last randomization, October 2020 (or have died/become lost to follow-up before 5 years). Events of second primary malignancy 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 of the diagnosis of the second primary malignancy must be provided at the time of reporting as a serious adverse event (eg, any confirmatory histology or cytology results).

Grade 4 hematologic abnormalities are expected in patients with CLL, and are also observed in patients receiving lenalidomide. The investigator will use their judgement to classify the seriousness of laboratory abnormality events. Laboratory values will be captured within the study database and will be reviewed on an ongoing basis by the sponsor and (provided that it is determined that any observed individual abnormalities or patterns of abnormalities do not warrant prompt communication to Heath Authorities) will be reported to Health Authorities in periodic safety reports.

The SAE must be reported (ie, within 24 hours of the Investigators' knowledge of the event) to the Celgene Safety by facsimile. An initial written report (prepared by the Investigator(s) using the SAE Report Form provided by Celgene) is to be faxed to the Safety Monitor (see below for contact information).

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

The Investigator(s) is responsible for informing the Institutional Review Board/Ethics Committee (IRB/IEC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator(s) must keep copies of all SAE information, including correspondence with Celgene and the IRB/IEC, on file. All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until either the event resolves completely, stabilizes/resolves with sequelae, or returns to baseline (if a baseline value is available).

Pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject or the female partner of a male subject occurring while the subject is on study drug, or within 28 days of the treatment discontinuation visit, are considered immediately reportable events. Study drug is to be discontinued immediately and the subject instructed to return any unused portion of the study drug to the investigator(s). The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Celgene Safety Monitor immediately by facsimile using the SAE Report Form.

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

The Investigator(s) will follow the female subject until completion of the pregnancy, and must notify Celgene Safety of the outcome of the pregnancy as a follow-up to the initial SAE report.

If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (ie, spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the Investigator(s) should follow the procedures for reporting SAEs (ie, report the event to Celgene Safety by facsimile within 24 hours of the Investigator's knowledge of the event).

In the case of a live "normal" birth, the Celgene Safety Monitor should be advised by telephone and facsimile within 24 hours of the Investigator's knowledge of the event.

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator(s) suspects is related to the in utero exposure to the study drug should also be reported to Celgene Safety by facsimile within 24 hours of the Investigators' knowledge of the event.

If the female is found not to be pregnant, any determination regarding the subject's continued participation in the study will be determined by the Investigator(s) and the Celgene Medical Monitor.

Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of reported events suspected of being related to lenalidomide based on the Investigator Brochure. Celgene Global Drug Safety will use the German Summary of Product Characteristics (SmPC) as the safety reference document for allopurinol.

For countries within the European Union, Celgene will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, AEs in accordance with the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

Celgene shall notify the Investigator of the following information:

- Any AE associated with the use of study drug in this study or in other studies that is both serious and unexpected, ie, suspected unexpected serious adverse reaction (SUSAR). Note that such cases from blinded studies will be unblinded for reporting purposes.
- Any finding from tests in laboratory animals that suggests a significant risk for human study subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

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

The Investigator must keep copies of all pertinent safety information, including correspondence with Celgene and the IRB/IEC, on file (see Section 19.3 for records retention information).

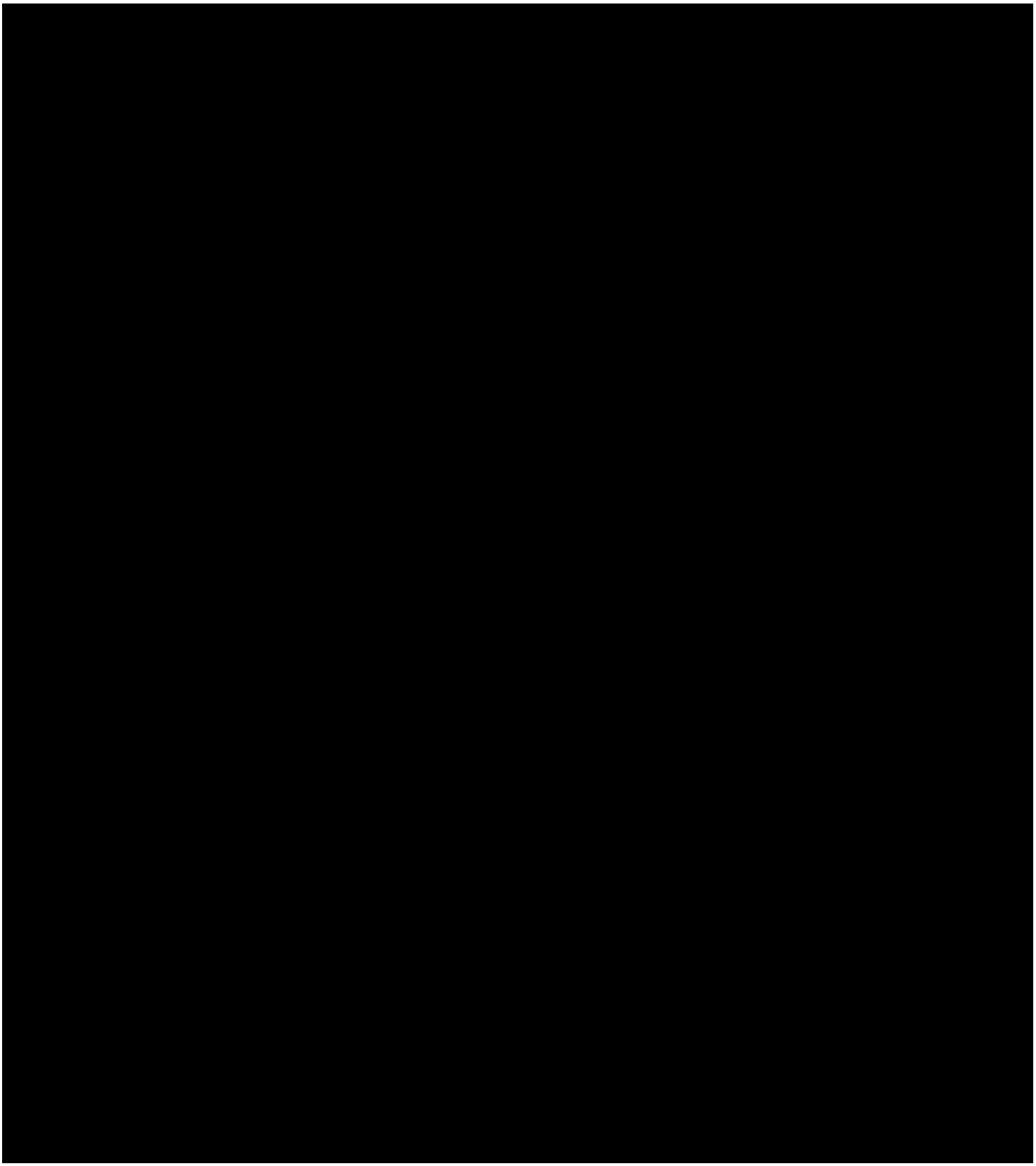
23.2. Declaration of Helsinki

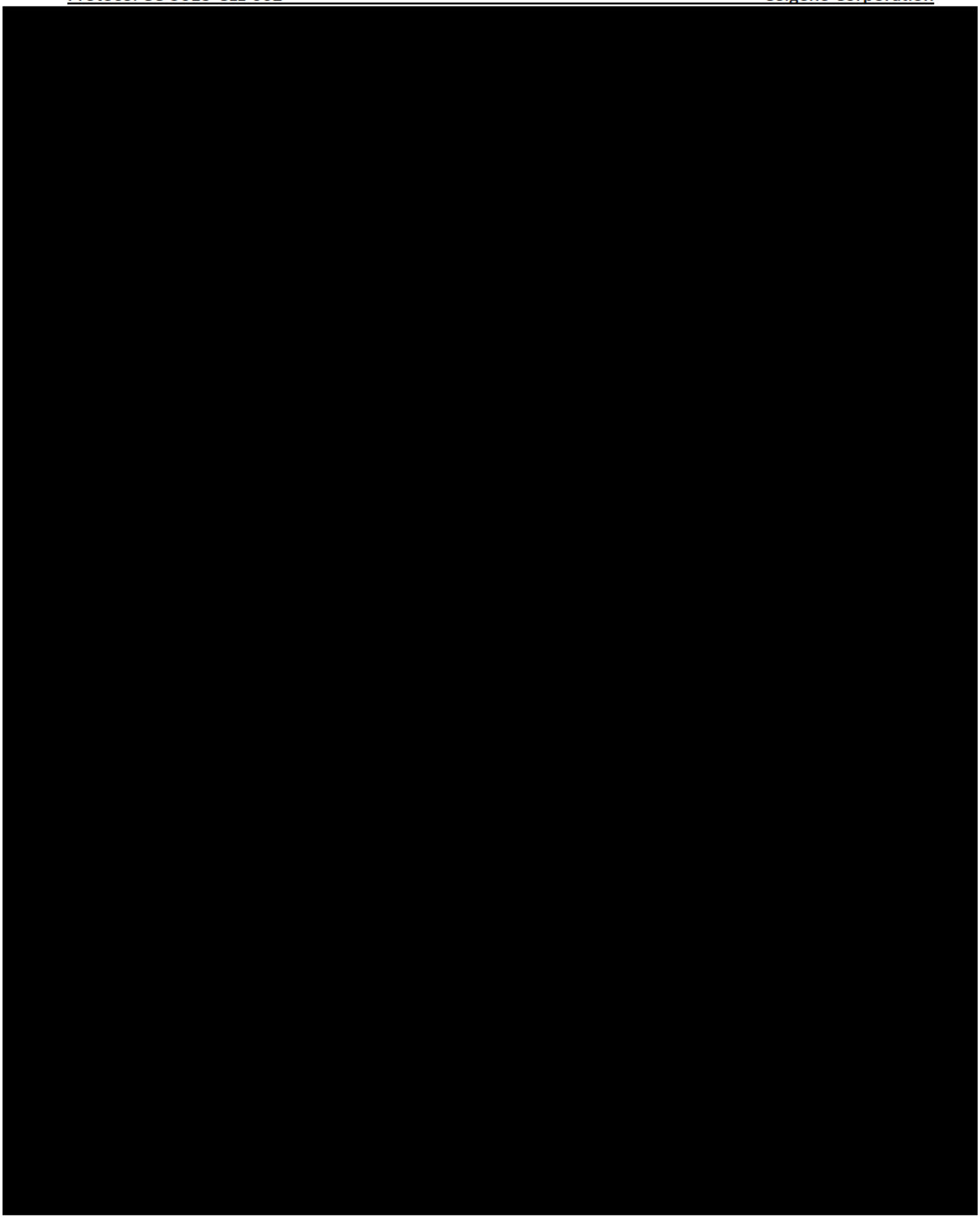
Celgene operates in accordance with the general ethical principles outlined in the Declaration of Helsinki.

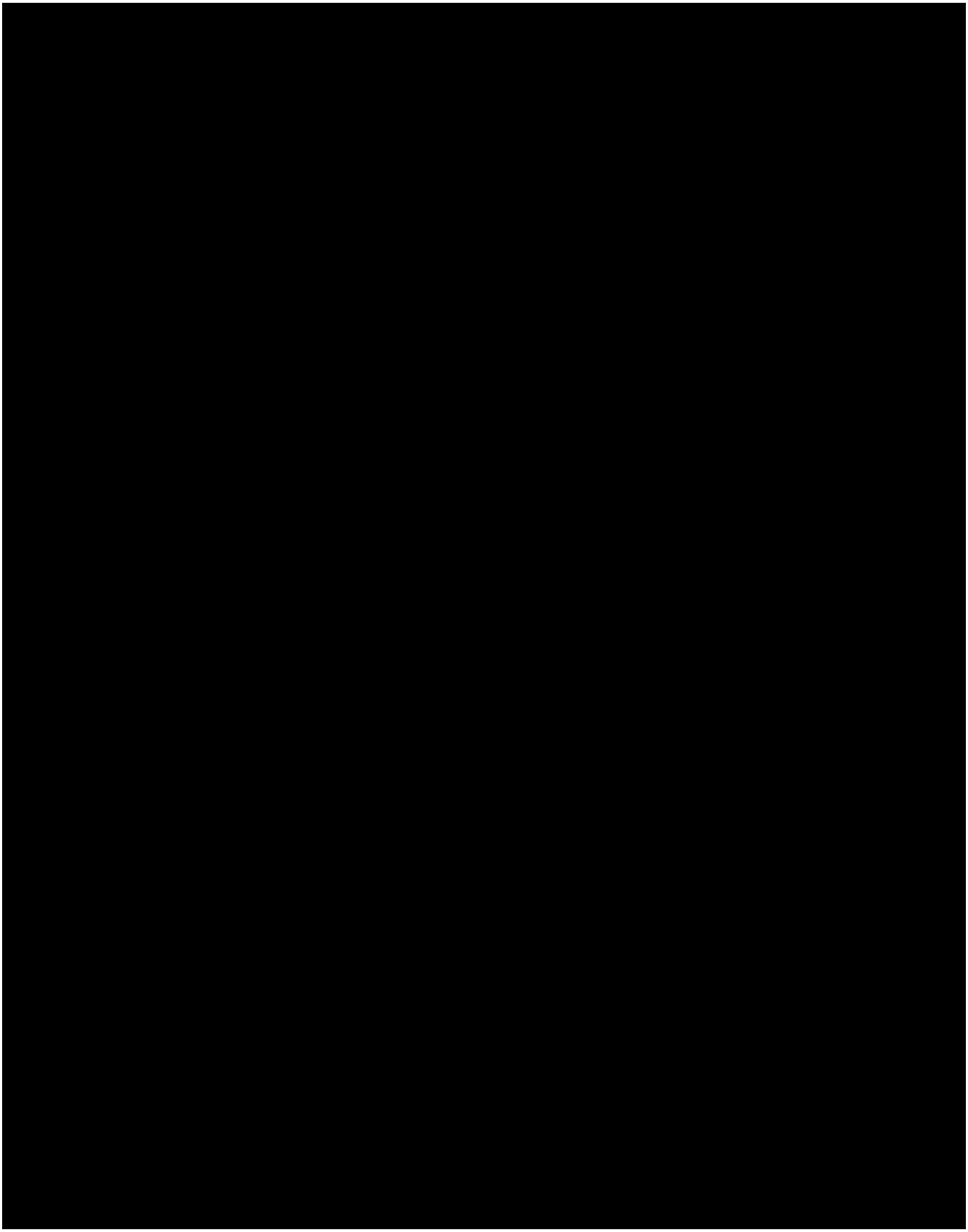
23.3. ECOG Performance Status Scale

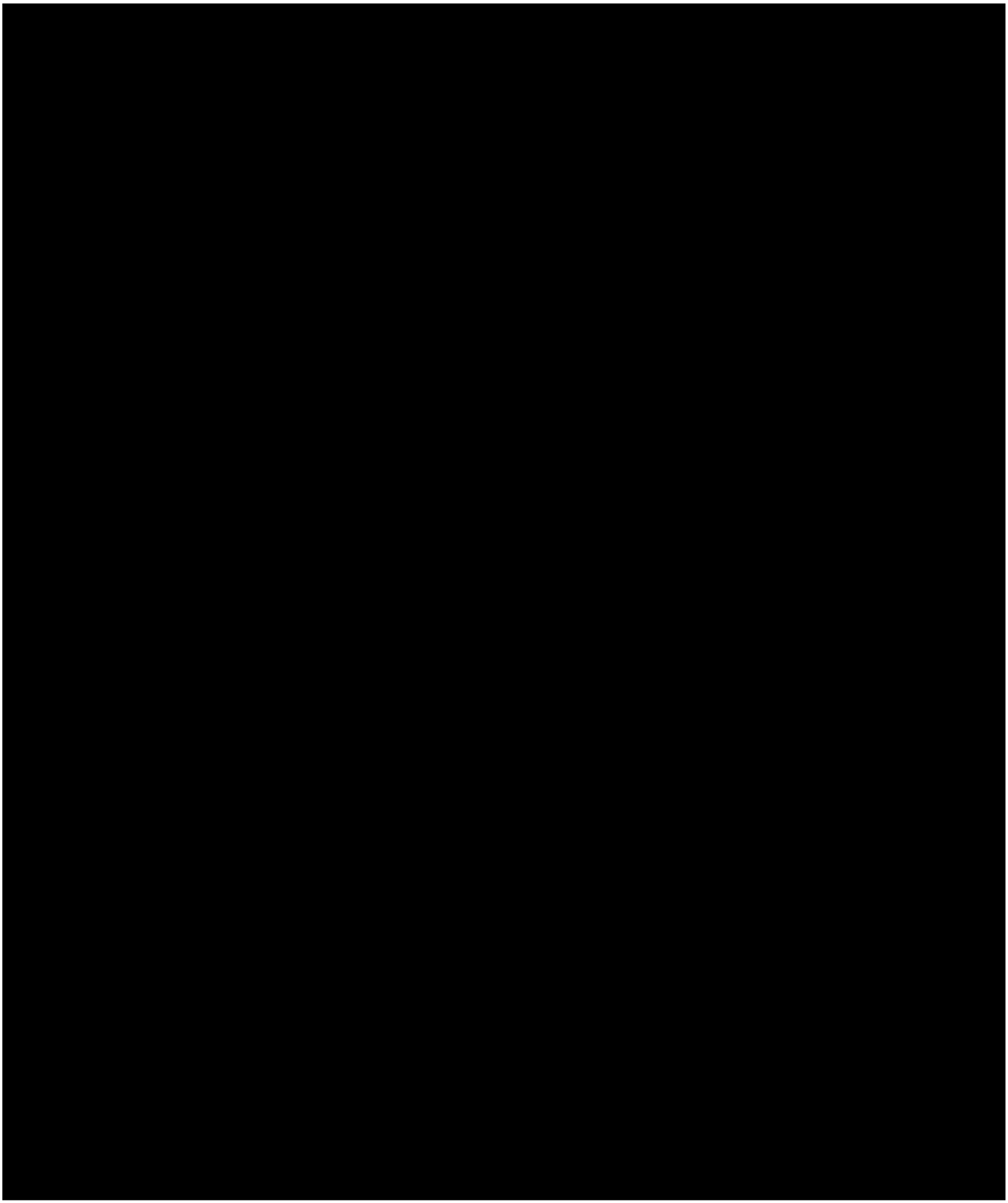
Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry our work of a light or sedentary nature, eg, light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

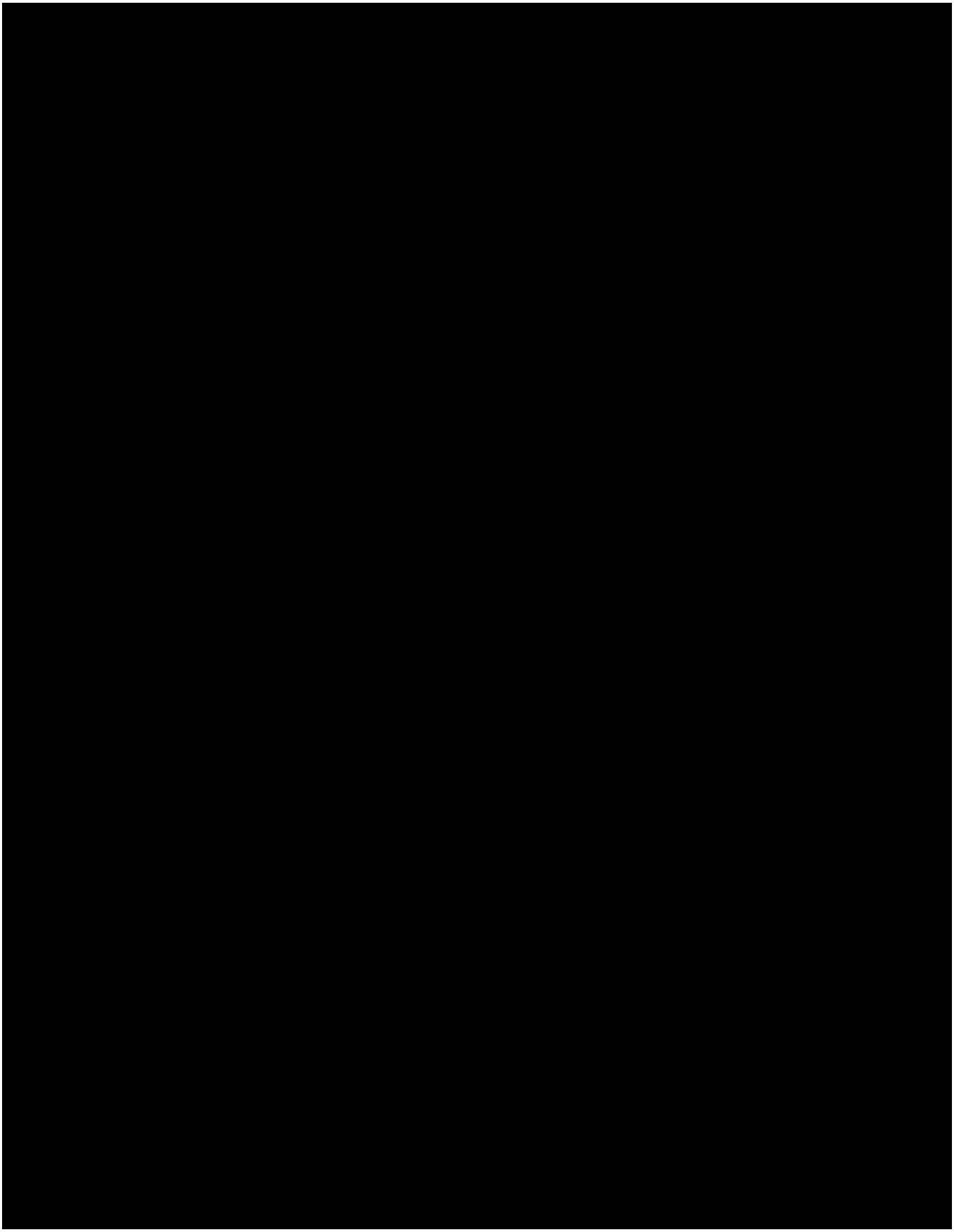
[redacted]

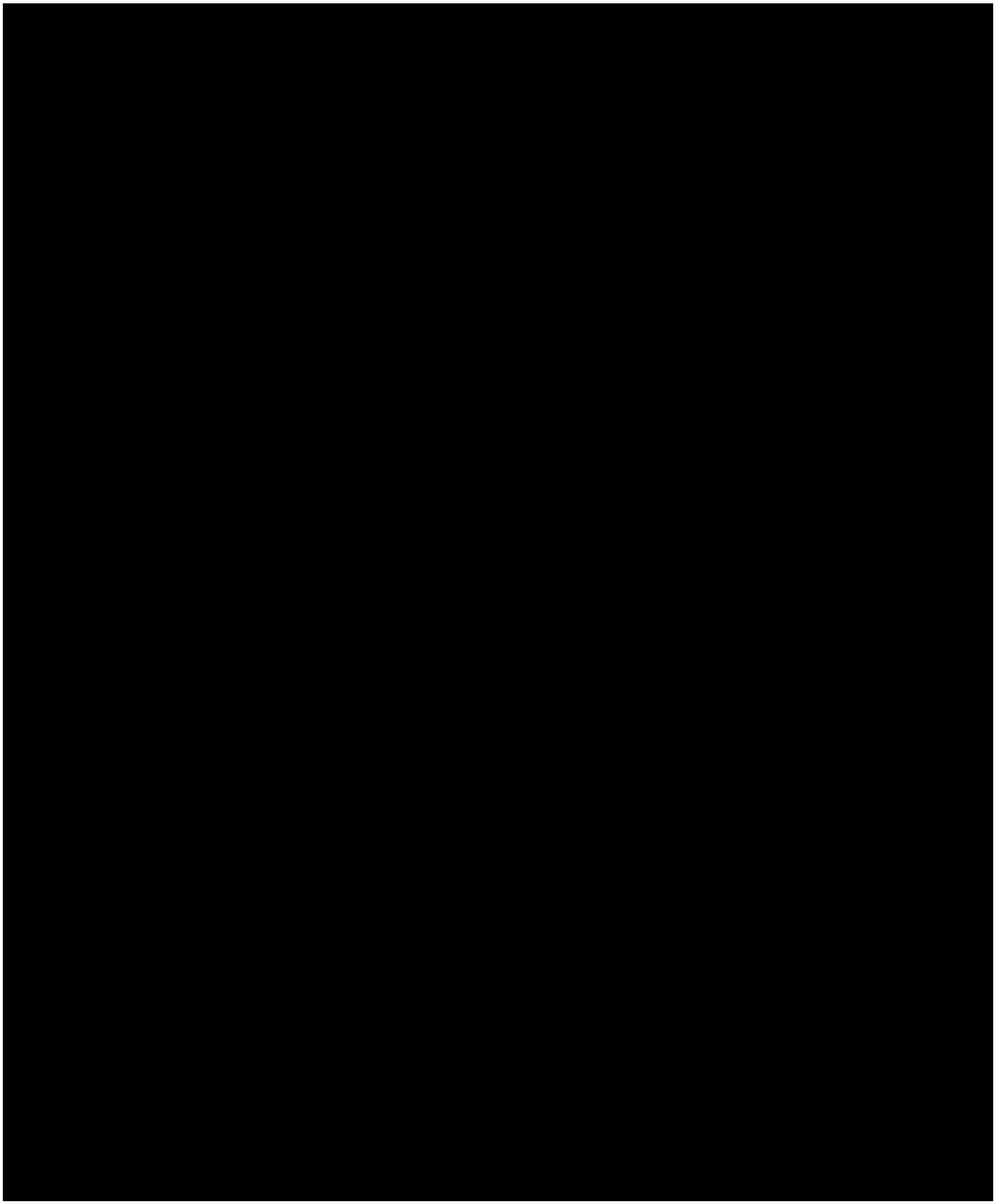












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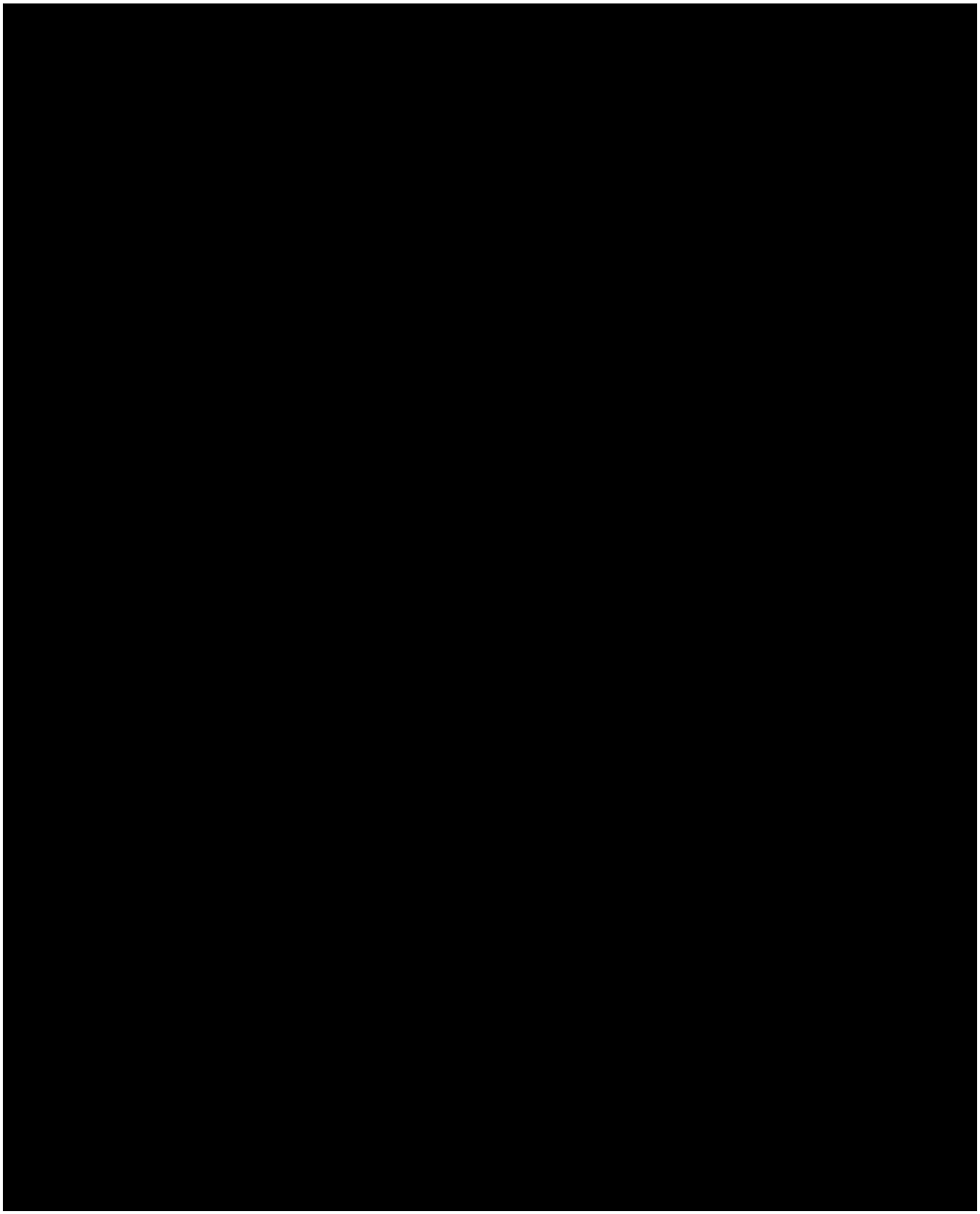

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23.6. Pregnancy Prevention Risk Management Plans

23.6.1. Lenalidomide Pregnancy Prevention Risk Management Plan

23.6.1.1. Lenalidomide Pregnancy Risk Minimisation Plan for Celgene Clinical Trials

Appendix 22.6.1 applies to all patients receiving lenalidomide therapy. The following Pregnancy Risk Minimisation Plan documents are included in this appendix:

1) Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods (Section 22.6.2);

2) Lenalidomide Education and Counseling Guidance Document (Section 22.6.2.1);

3) Lenalidomide Information Sheet (Section 22.6.2.2).

1. The Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods document (Section 22.6.2) provides the following information:
   - Potential risks to the fetus associated with lenalidomide exposure
   - Definition of Female of Childbearing Potential
   - Pregnancy testing requirements for patients receiving Lenalidomide who are females of childbearing potential
   - Acceptable birth control methods for both female of childbearing potential and male patients receiving Lenalidomide in the study
   - Requirements for counseling of all study patients receiving Lenalidomide about pregnancy precautions and the potential risks of fetal exposure to lenalidomide
2. The Lenalidomide Education and Counseling Guidance Document (Section 22.6.2.1) must be completed and signed by either a trained counselor or the Investigator at the participating clinical center prior to each dispensing of lenalidomide study treatment. A copy of this document must be maintained in the patient records.
3. The Lenalidomide Information Sheet (Section 22.6.2.2) will be given to each patient receiving lenalidomide study therapy. The patient must read this document prior to starting lenalidomide study treatment and each time they receive a new supply of study drug.

23.6.2. Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods

Risks Associated with Pregnancy

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

Criteria for females of childbearing potential (FCBP)

This protocol defines a female of childbearing potential as a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

Counseling

For a female of childbearing potential, lenalidomide is contraindicated unless all of the following are met (ie, all females of childbearing potential must be counseled concerning the following risks and requirements prior to the start of lenalidomide study therapy):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 4 weeks before starting study treatment, throughout the entire duration of study treatment, dose interruption and 28 days after the end of study treatment
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence the study treatment as soon as study drug is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing based on the frequency outlined in this protocol (Section 22.6.2)
- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide

The investigator must ensure that for females of childbearing potential:

- Complies with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding
- Acknowledge the aforementioned requirements

For a female NOT of childbearing potential, lenalidomide is contraindicated unless all of the following are met (ie, all females NOT of childbearing potential must be counseled concerning the following risks and requirements prior to the start of lenalidomide study therapy):

- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide

Traces of lenalidomide have been found in semen. Male patients taking lenalidomide must meet the following conditions (ie, all males must be counseled concerning the following risks and requirements prior to the start of lenalidomide study therapy):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a female of childbearing potential
- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a female of childbearing potential.

Contraception

Females of childbearing potential (FCBP) enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting study drug; 2) while participating in the study; 3) dose interruptions; and 4) for at least 28 days after study treatment discontinuation.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. FCBP must be referred to a qualified provider of contraceptive methods if needed. The following are examples of highly effective and additional effective methods of contraception:

- Highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants)
  - Tubal ligation
  - Partner's vasectomy
- Additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for females of childbearing potential, including females of childbearing potential who commit to complete abstinence, as outlined below.

Before starting study drug

Female Patients:

FCBP must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 10 to 14 days prior to the start of study drug and the second pregnancy test must be performed within 24 hours prior to the start of study drug. The patient may not receive study drug until the study doctor has verified that the results of these pregnancy tests are negative.

Male Patients:

Must practice complete 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 study drug discontinuation, even if he has undergone a successful vasectomy.

During study participation and for 28 days following study drug discontinuation

Female Patients:

- 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 study drug 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 study drug discontinuation.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days. If pregnancy or a positive pregnancy test does occur in a study patient, study drug must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a patient misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Study drug treatment must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after study drug discontinuation.

Male Patients:

- Counseling about the requirement for complete abstinence or condom use during sexual contact with a pregnant female or a female of childbearing potential and the

potential risks of fetal exposure to lenalidomide must be conducted at a minimum of every 28 days.

- If pregnancy or a positive pregnancy test does occur in the partner of a male study patient during study participation, the investigator must be notified immediately.

Additional precautions

- Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to the study doctor at the end of treatment.
- Female patients should not donate blood during therapy and for at least 28 days following discontinuation of study drug.
- Male patients should not donate blood, semen or sperm during therapy or for at least 28 days following discontinuation of study drug.
- Only enough study drug for one cycle of therapy may be dispensed with each cycle of therapy.

23.6.2.1. Lenalidomide Education and Counseling Guidance Document

To be completed prior to each dispensing of study drug.

Protocol Number: _____

Patient Name (Print): _____ DOB: _____/_____/_____ (mm/dd/yyyy)

(Check the appropriate box to indicate risk category)

Female: □

If female, check one:

- ❑ FCBP (Female of childbearing potential): sexually mature female who: 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time during the preceding 24 consecutive months)
- ❑ NOT FCBP

Male: □

Do Not Dispense study drug if:

- The patient is pregnant.
- No pregnancy tests were conducted for a FCBP.
- The patient states she did not use TWO reliable methods of birth control (unless practicing complete abstinence of heterosexual contact) [at least 28 days prior to therapy, during therapy and during dose interruption].

FCBP:

1. I verified that the required pregnancy tests performed are negative.
2. I counseled FCBP regarding the following:
   - Potential risk of fetal exposure to lenalidomide: If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking lenalidomide. The teratogenic potential of lenalidomide in humans cannot be ruled out. FCBP must agree not to become pregnant while taking lenalidomide.
   - Using TWO reliable methods of birth control at the same time or complete abstinence from heterosexual contact [at least 28 days prior to therapy, during therapy, during dose interruption and 28 days after discontinuation of study drug].
   - That even if she has amenorrhea she must comply with advice on contraception.

- Use of one highly effective method and one additional method of birth control AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:
  - Highly effective methods:
    - Intrauterine device (IUD)
    - Hormonal (birth control pills, injections, implants)
    - Tubal ligation
    - Partner's vasectomy
  - Additional effective methods:
    - Male condom
    - Diaphragm
    - Cervical Cap
- Pregnancy tests before and during treatment, even if the patient agrees not to have reproductive heterosexual contact. Two pregnancy tests will be performed prior to receiving study drug, one within 10 to 14 days and the second within 24 hours of the start of study drug.
- Frequency of pregnancy tests to be done:
  - Every week during the first 28 days of this study and a pregnancy test every 28 days during the patient's participation in this study if menstrual cycles are regular or every 14 days if cycles are irregular.
  - If the patient missed a period or has unusual menstrual bleeding.
  - When the patient is discontinued from the study and at day 28 after study drug discontinuation if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at days 14 and 28 after study drug discontinuation.
- Stop taking study drug immediately in the event of becoming pregnant and to call their study doctor as soon as possible.
- NEVER share study drug with anyone else.
- Do not donate blood while taking study drug and for 28 days after stopping study drug.
- Do not breastfeed a baby while participating in this study and for at least 28 days after study drug discontinuation.
- Do not break, chew, or open study drug capsules.
- Return unused study drug to the study doctor.

3. Provide Lenalidomide Information Sheet to the patient.

FEMALE NOT OF CHILDBEARING POTENTIAL (NATURAL MENOPAUSE FOR AT LEAST 24 CONSECUTIVE MONTHS, A HYSTERECTOMY, OR BILATERAL OOPHORECTOMY):

1. I counseled the female NOT of child bearing potential regarding the following:
   - Potential risks of fetal exposure to lenalidomide (Refer to item #2 in FCBP)
   - NEVER share study drug with anyone else.
   - Do not donate blood while taking study drug and for 28 days after stopping study drug.
   - Do not break, chew, or open study drug capsules.
   - Return unused study drug capsules to the study doctor.
2. Provide Lenalidomide Information Sheet to the patient.

MALE:

1. I counseled the Male patient regarding the following:
   - Potential risks of fetal exposure to lenalidomide (Refer to item #2 in FCBP).
   - To engage in complete abstinence or use a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or a female of childbearing potential, while taking study drug, during dose interruptions and for 28 days after stopping study drug.
   - Males should notify their study doctor when their female partner becomes pregnant and female partners of males taking study drug should be advised to call their healthcare provider immediately if they get pregnant.
   - NEVER share study drug with anyone else.
   - Do not donate blood, semen or sperm while taking study drug and for 28 days after stopping study drug.
   - Do not break, chew, or open study drug capsules.
   - Return unused study drug capsules to the study doctor.
2. Provide Lenalidomide Information Sheet to the patient.

Investigator/Counselor Name (Print): _____

(circle applicable)

Investigator/Counselor Signature: _____ Date: _____/_____/_____

(circle applicable)

Maintain a copy of the Education and Counseling Guidance Document in the patient records.

23.6.2.2. Lenalidomide Information Sheet

FOR PATIENTS ENROLLED IN CLINICAL RESEARCH STUDIES

Please read this Lenalidomide Information Sheet before you start taking study drug and each time you get a new supply. This Lenalidomide Information Sheet does not take the place of an informed consent to participate in clinical research or talking to your study doctor or healthcare provider about your medical condition or your treatment.

What is the most important information I should know about lenalidomide?

1. **Lenalidomide may cause birth defects (deformed babies) or death of an unborn baby.** Lenalidomide is similar to the medicine thalidomide. It is known that thalidomide causes life-threatening birth defects. Lenalidomide has not been tested in pregnant women but may also cause birth defects. Findings from a monkey study indicate that lenalidomide caused birth defects in the offspring of female monkeys who received the drug during pregnancy.

   If you are a female who is able to become pregnant:

   - **Do not take study drug if you are pregnant or plan to become pregnant**
   - **You must practice complete abstinence or use two reliable, separate forms of effective birth control at the same time:**
     - for 28 days before starting study drug
     - while taking study drug
     - during dose interruptions of study drug
     - for 28 days after stopping study drug
   - **You must have pregnancy testing done at the following times:**
     - within 10 to 14 days and again 24 hours prior to the first dose of study drug
     - weekly for the first 28 days
     - every 28 days after the first month or every 14 days if you have irregular menstrual periods
     - if you miss your period or have unusual menstrual bleeding
     - 28 days after the last dose of study drug (14 and 28 days after the last dose if menstrual periods are irregular)
   - **Stop taking study drug if you become pregnant during treatment**
     - If you suspect you are pregnant at any time during the study, you must stop study drug immediately and immediately inform your study doctor. Your study doctor will report all cases of pregnancy to Celgene Corporation
   - **Do not breastfeed while taking study drug**

- The study doctor will be able to advise you where to get additional advice on contraception.

If you are a female not of childbearing potential:

In order to ensure that an unborn baby is not exposed to lenalidomide, your study doctor will confirm that you are not able to become pregnant.

If you are a male:

Lenalidomide is detected in trace quantities in human semen. The risk to the foetus in females of childbearing potential whose male partner is receiving lenalidomide is unknown at this time.

- Male patients (including those who have had a vasectomy) must practice complete abstinence or must use a condom during sexual contact with a pregnant female or a female that can become pregnant:
  - While you are taking study drug
  - During dose interruptions of study drug
  - For 28 days after you stop taking study drug
- **Male patients should not donate sperm or semen** while taking study drug and for 28 days after stopping study drug.
- **If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation. Your partner should call their healthcare provider immediately if they get pregnant.**

2. **Restrictions in sharing study drug and donating blood:**
   - **Do not share study drug with other people. It must be kept out of the reach of children and should never be given to any other person.**
   - **Do not donate blood** while you take study drug and for 28 days after stopping study drug.
   - **Do not break, chew, or open study drug capsules.**
   - You will get no more than a 28-day supply of study drug at one time.
   - Return unused study drug capsules to your study doctor.

Additional information is provided in the informed consent form and you can ask your study doctor for more information.