DISCLOSURE

REDACTED PROTOCOL AMENDMENT 6

CC-5013-CLL-009

A Phase 2, Multi-Center, Randomized, Double-Blind, Parallel-Group Study Of The Safety And Efficacy Of Different Lenalidomide (Revlimid®) Dose Regimens In Subjects With Relapsed Or Refractory B-Cell Chronic Lymphocytic Leukemia

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A PHASE 2, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP STUDY OF THE SAFETY AND EFFICACY OF DIFFERENT LENALIDOMIDE (REVLIMID®) DOSE REGIMENS IN SUBJECTS WITH RELAPSED OR REFRACTORY B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA

STUDY DRUG:	Lenalidomide
PROTOCOL NUMBER:	CC-5013-CLL-009
EudraCT NUMBER	2009-009836-54
DATE FINAL:	09 March 2009
AMENDMENT #1	10 June 2009
AMENDMENT #2	11 February 2010
AMENDMENT #3	9 December 2010
AMENDMENT #4	12 May 2011
AMENDMENT #5	9 November 2011
AMENDMENT #6	15 April 2015

_____*{See appended electronic signature page}*_____
Signature of Celgene Therapeutic Area Head

_____ _____
Printed Name of Celgene Therapeutic Area Head

Date Signed _____

dd mmm yyyy

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COORDINATING PRINCIPAL INVESTIGATOR SIGNATURE PAGE

[include if applicable]

Signature of Coordinating Principal Investigator **dd mmm yyyy**

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, IRB/EC procedures, instructions from Celgene representatives, the Declaration of Helsinki, ICH Good Clinical Practice 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

Signature of Site Principal Investigator **dd mmm yyyy**

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/EC procedures, instructions from Celgene representatives, the Declaration of Helsinki, ICH Good Clinical Practice guidelines, and the applicable parts of the United States Code of Federal Regulations and local regulations governing the conduct of clinical studies.

1. STUDY CONTACT INFORMATION

Table 1: Celgene Emergency Contact Information

Role in Study	Name	Address and Telephone Number
		Celgene International Sàrl Celgene R&D Route de Perreux 1 2017 Boudry, Switzerland Telephone: Email:
		Celgene International Sàrl Celgene R&D Route de Perreux 1 2017 Boudry, Switzerland Telephone: Mobile: Email:
Drug Safety Contact **Contact information for the local reporting of SAEs will be provided in a separate document.	Global Drug Safety International	Celgene Corporation Telephone: Fax: E-mail: drugsafety@celgene.com Celgene Global Drug Safety Celgene International Sàrl Route de Perreux 1 2017 Boudry, Switzerland Telephone: Fax: Email:

Table 1: Celgene Emergency Contact Information (Continued)

Role in Study	Name	Address and Telephone Number
		Celgene International Sàrl Celgene R&D Route de Perreux 1 2017 Boudry, Switzerland Telephone: Mobile: Email:
		Telephone: Mobile: Email:

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

Back-up 24 Hour Global Emergency Contact Call Center: +1-877-501-7738

2. SYNOPSIS

Name of Sponsor/Company: Celgene Corporation	
Name of Investigational Product: lenalidomide	
Protocol Number: CC-5013-CLL-009	
Protocol Title: A Phase 2, Multi-Center, Randomized, Double-Blind, Parallel-Group Study Of The Safety And Efficacy Of Different Lenalidomide (Revlimid®) Dose Regimens In Subjects With Relapsed Or Refractory B-Cell Chronic Lymphocytic Leukemia	
Indication: For the treatment of patients with B-cell chronic lymphocytic leukemia who have failed at least 1 prior therapy	
Study Duration: Subjects may receive study drug until disease progression or unacceptable toxicity develops, whichever occurs first. Study will be closed once 80% of the subjects randomized to the study have progressed or died or up to five years after the last subject was randomized, whichever occurs later. All subjects ongoing on study drug at the time the study is closed will be transferred to lenalidomide on a free basis in agreement with the site principal investigator and according to local regulations.	**Phase of development:** Phase 2
Objectives **Primary** • To evaluate the safety of different lenalidomide dose regimens in subjects with relapsed or refractory B-cell CLL. **Secondary** • To evaluate the efficacy of different lenalidomide dose regimens in subjects with relapsed or refractory B-cell CLL.	
Study Endpoints **Primary** • Safety [type, frequency, and severity of adverse events (AEs) and relationship of AEs to lenalidomide] **Secondary**	

- Response rate; International Workshop on Chronic Lymphocytic Leukemia (iwCLL) Guidelines for the diagnosis and treatment of CLL (Hallek, 2008)
- Duration of response
- Time to response (TTR)
- Time to progression (TTP)
- Event-free survival (EFS)
- Progression-free survival (PFS)
- Overall survival (OS)

Exploratory

- Evaluation of response rate in predefined biologic risk group
-
- Investigate the relationship between pharmacokinetics (PK) and response (biomarkers or clinical outcomes as appropriate)
- Quality of Life

Study Design

CC-5013-CLL-009 is a phase 2, multi-center, randomized, double-blind, parallel-group adaptive design study that will evaluate the safety and efficacy of different lenalidomide dose regimens administered orally. All regimens use a stepwise dose escalation scheme with three different initial ascending starting dose of 5 mg daily, 10 mg daily and 15 mg daily and then escalating in a stepwise manner every 28 days to reach a maximum dose of 25 mg daily based on subject tolerability. Approximately 105 subjects will be enrolled. Eligible subjects must have B-cell CLL that has relapsed after or is refractory to at least one prior CLL treatment regimen. At least one of the prior treatments must have included a purine-analog or bendamustine based treatment regimen. Subjects must have active disease per the iwCLL Guidelines for the diagnosis and treatment of CLL (Hallek, 2008).

At the time of randomization, study subjects will be stratified by the following criteria:

- Relapsed vs. refractory to their last purine-analog or bendamustine based treatment regimen [relapsed/refractory as defined per the iwCLL guidelines for diagnosis and treatment of CLL (Hallek, 2008)]. If subject has received both, the status post most recent purine-analog or bendamustine regimen will be used for stratification.
- Age < 65 years of age vs. ≥ 65 years of age

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 initiating study drug as outlined in Table 2.

During screening all subjects will have the following assessments / samples collected:

- Vital signs, including height and weight
- Pregnancy testing as specified in Appendix 21.9
- Pregnancy and risk counseling as specified in Appendix 21.9
- Assessment of ECOG performance score
- Assessments of constitutional symptoms
- Physical examination to assess the lymph nodes, spleen and liver
- Clinical staging using Rai and /or Binet as defined per the iwCLL guidelines for diagnosis and treatment of CLL (Hallek, 2008) in Appendix 21.4
- 12-lead ECG
- Peripheral blood smear, bone marrow aspirate and bone marrow biopsy (reference samples) for central pathology reviewer (local pathology results will also be captured on the eCRFs).
- Peripheral blood for disease confirmation by immunophenotyping per Hallek, 2008.
- Peripheral blood sample for complete blood counts (CBCs), serum chemistries and thyroid function tests
- Urine sample for urinalysis
- Calculated (method of Cockroft-Gault) creatinine clearance (creatinine clearance may also be obtained by the 24-hour collection method at the investigator's discretion)
- Peripheral blood sample for a direct antiglobulin test (DAT)
- CT scans of the neck, chest, abdomen and pelvis to assess lymphadenopathies

Local/Central Laboratories and Reviewers

Data generated by central laboratories and evaluations performed by central pathology reviewer will prevail over locally generated information in the evaluation of the subject's efficacy results.

Laboratory tests that may result in dose interruption and/or modification as specified in Table 5 should also be performed locally to allow for treatment related decisions during subject visits.

At a minimum the following hematology/chemistry assessments must be performed locally: hemoglobin, absolute lymphocyte count, absolute neutrophil count and platelet count, potassium, calcium, phosphorus, creatinine, total bilirubin, AST/SGOT, ALT/SGPT, and uric acid.

At screening, subjects must meet eligibility criteria based on central lab results. At Study Day 1, subjects must meet eligibility criteria based on local or central lab results prior to initiating study therapy, however, a re-calculation of creatinine clearance is not required at Study Day 1.

Exploratory Assessments

The following exploratory assessments will be performed in all subjects:

- Blood samples for ZAP-70, V_H mutational status /TP53 mutation analysis, FISH studies for cytogenetic assessment, will be collected at baseline.

Subjects will complete quality of life questionnaire (FACT-Leu and EQ-5D questionnaires) at time points detailed in Table 2.

Pharmacokinetic assessments

Pharmacokinetic assessments will be performed in up to 40 subjects who provide consent at select centers. Intensive sampling and sparse sampling will be discontinued as of this amendment, protocol amendment #6.

Treatment

Subjects must meet all eligibility criteria to be randomized for the study.

Initial randomization

Initially subjects will be randomized (1:1:1) in a double-blind fashion to the 5 mg, 10 mg, and 15 mg starting dose arms (treatment arm 1, treatment arm 2, and treatment arm 3 respectively). The randomization procedure will be accomplished by a validated interactive voice response system (IVRS). Subjects will be stratified at randomization by (i) relapsed vs refractory to their last purine-analog or bendamustine based treatment regimen (if subject has received both, the status post most recent purine-analog or bendamustine regimen will be used for stratification) and (ii) age < 65 years of age vs ≥ 65 years of age. The subjects will receive lenalidomide once daily in a 28 day cycle and will be escalated every 28 days as tolerated in a stepwise manner up to a maximum of 25 mg daily.

Stopping of Treatment Arm(s)

After 18 subjects complete one 28 day cycle, an interim analysis will be conducted to review the safety of each starting dose arm(s). Subsequent interim analyses to review the safety and progression rate of each starting dose arm(s) will occur at 13-week intervals. After review of each interim analysis, a treatment arm may be dropped. At any time accrual to a starting dose arm will also be stopped if unacceptable toxicities are observed in that arm. If a treatment arm is dropped then all new subjects will be randomized equally into the remaining arm(s).

Dose Regimens:

Depending on the starting dose, subjects will be allocated in a double-blind fashion to three different regimens and will escalate every 28 days, based on individual subject tolerability, as follows:

- Treatment Arm 1: 5 mg →10 mg →15 mg →20 mg →25 mg/daily
- Treatment Arm 2: 10 mg →15 mg →20 mg →25 mg/daily
- Treatment Arm 3: 15 mg →20 mg →25 mg/daily

For toxicities requiring dose interruption and/or modification see Section 10.2.3. Note that a more gradual stepwise dose escalation of lenalidomide (more than one 28 day cycle for each dose level) might be needed at the discretion of the treating physician due to adverse events that do not require dose reduction or interruption.

Subjects unable to escalate to the 25 mg maximum dose due to toxicity may continue with the highest dose achieved in the previous cycle or as indicated in the dose modification section (see Section 10.2.3).

Study visits and serial measurements of safety and efficacy will be performed as outlined in Table 2. The severity of adverse events (AEs) will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0 with the exceptions of hematological toxicities and TLS. Hematological toxicities will be graded as specified in the iwCLL guidelines for the diagnosis and treatment of chronic lymphocytic leukemia (Hallek, 2008) (Appendix 21.4). TLS will be graded as specified by the Cairo-Bishop grading system (Appendix 21.3).

The use of hematopoietic growth factors is permitted. Treatment with myeloid growth factors is strongly encouraged following ASCO guidelines recommendation (Smith, 2006) for dosing and administration when the absolute neutrophil count (ANC) is less than 1,000/μL [NOTE: per the inclusion criteria, subjects must have an ANC ≥ 1000/μL to be eligible for study entry].

Subjects will continue in the study and receive study drug until discontinuation from the study for any of the following reasons: disease progression; AEs that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of study drug, subject withdraws consent, subject is lost to follow-up, death, protocol violation that may rule out continuation of study drug and other reasons that in the judgment of the Investigator may rule out continuation of study drug.

For those subjects who discontinue study drug for reasons other than disease progression or withdrawal of consent, study visits should continue every 28 days to assess response until documentation of disease progression or until a new CLL therapeutic regimen is started, whichever comes first. During these visits only the following assessments will be required: hematology, ECOG performance status, evaluation of constitutional symptoms, physical exam for liver, spleen and lymph nodes, adverse events, assessment for second primary malignancies, concomitant medications/therapies, and assessment of response.

For subjects who develop PD characterized by transformation to a more aggressive histology [i.e. Richter's syndrome (lymphomas) or prolymphocytic leukemia], this diagnosis should be established by lymph node biopsy whenever possible.

Subjects who are discontinued from the study drug for any reason, except for withdrawal of

consent, will be followed every 12 weeks for survival, secondary primary malignancies and subsequent CLL therapies until the study is closed (see Figure 1 Overall Study Schema).

Study will be closed once 80% of the subjects randomized to the study have progressed or died or up to five years after the last subject was randomized, whichever occurs later. All subjects ongoing on study drug at the time the study is closed will be transferred to lenalidomide on a free basis in agreement with the site principal investigator and local regulations.

Response Assessment

Tumor response will be assessed according to the iwCLL guidelines for the diagnosis and treatment of CLL (Hallek, 2008), including CR, CRi, nPR, PR, SD and PD. Evaluation of response will be performed after 3 cycles of therapy and every 4 weeks thereafter.

For those subjects who reach PR, CRi or CR, a CT scan of the neck, chest, abdomen and pelvis to assess lymphadenopathies will be performed at the PR and CR/CRi confirmation visits (≥ 8 weeks to ≤ 12 weeks)after all clinical and laboratory response criteria have been met for PR or CR/CRi). Those subjects whose response was down-graded based on the CT scan interpretation at the PR or CR/CRi confirmation visit will have the CT scan repeated 4 months later at the location where remaining disease has been documented, as long as clinical and laboratory response remains present to try to document further improvement.

For those subjects who reach CR or CRi, a bone marrow aspirate and bone marrow biopsy will be performed at the CR/CRi confirmation visit (≥ 8 weeks to ≤ 12 weeks after all clinical and laboratory response criteria have been met). If the bone marrow is hypocellular, a repeat specimen should be obtained after 4 weeks, provided that the blood counts have recovered. If the bone marrow biopsy shows disease involvement (30% or greater lymphocytes, or nodules positive for B-CLL cells by immunohistochemistry), an additional bone marrow biopsy and aspirate will be taken 4 months later as long as clinical and laboratory response remain in CR or CRi response status to try to document further improvement.

MRD status will be evaluated for those subjects who reach CR or CRi. A peripheral blood and bone marrow aspirate sample will be collected for MRD analysis by flow cytometry at the CR/CRi confirmation visit.

- If peripheral blood and bone marrow are both MRD-positive, peripheral blood samples will be repeated and assessed up to 3 additional times at 8 week intervals to try to document MRD negativity in subjects who reach confirmed CR or CRi (see Follow-up MRD assessments).
- If peripheral blood is MRD-negative and bone marrow is MRD-positive, both peripheral blood and bone marrow should be retested for MRD negativity after ≥ 12 weeks. If this repeat bone marrow is MRD-positive, no further testing for MRD will be performed.
- If both the peripheral blood and bone marrow are MRD-negative, peripheral blood will be tested every 6 months for assessment of MRD until subject discontinues study drug.

Follow-up MRD assessments:

- If any of the repeat peripheral blood assessments indicate MRD-negativity, a bone

marrow aspirate sample should be collected and retested as soon as possible to confirm MRD negativity.

- If the bone marrow is MRD-positive, both peripheral blood and bone marrow should be retested for MRD negativity after ≥ 12 weeks. If this repeat bone marrow is MRD-positive, no further testing for MRD will be performed.
- If at any time, the bone marrow is MRD-negative, peripheral blood will be tested every 6 months for assessment of MRD until subject discontinues study drug.

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

TLS and TFR

TLS prophylaxis, comprising of oral hydration and allopurinol 300 mg/day will be initiated at least 3 days prior to starting study drug and for a minimum of the first 3 treatment cycles. For subjects with known allergy to allopurinol prior to study initiation or for those who develop an allergy during the course of study, the medical monitor should be contacted. 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 each cycle during the dose escalation period. 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.

Grade 1 TFR may be treated with NSAIDs and TFR ≥ Grade 2 may be treated with corticosteroids. Narcotic analgesics may be added as needed for pain control in subjects experiencing ≥ Grade 2 TFR.

Subjects will be monitored for TLS and TFR as follows:

- On Day 2 and 4 and then weekly (Days 8, 15, 22) for cycle 1 and the first cycle of each dose escalation
- On Day 1, 8 and 15 of cycle 2 (if not dose escalated)
- At least every 28 days thereafter and as clinically indicated.

Thromboembolic Events Prophylaxis

Lenalidomide may increase the risk of thromboembolic events in subjects who are at high risk (high risk is defined for example as a history of a thromboembolic event and/or taking a concomitant medication associated with an increased risk for a thromboembolic event and/or a known hypercoagulable state regardless of thromboembolic history). All subjects should receive anti-thrombotic prophylaxis during study treatment. For subjects who enter the study with a platelet count close to the eligibility criteria of ≥ 50,000/ μL, the medical monitor should be contacted to discuss the anti-thrombotic prophylaxis. The recommended prophylaxis is low-dose aspirin [ASA] (70-100mg) daily; however, another prophylactic anti-thrombotic therapy may be used per investigator's discretion during study treatment. Choice of the most appropriate anti-thrombotic therapy for each subject should be based upon a careful evaluation of the different risk factors associated with each therapy, and a corresponding assessment of the individual subject's underlying medical condition. Selection should be based on the overall benefit-to-risk ratio. Use of low molecular weight heparin or warfarin (or equivalent Vitamin K

antagonist) to keep the International Normalization Ratio (INR) in the range of 2-3 or other anti-thrombotic therapy according to hospital guidelines or physician preference is acceptable.

If platelets drop below 50,000/μL, the investigator should consider interrupting or adjusting the dose of anti-thrombotic therapy. In the event that platelets drop below 20,000/μL and the anti-thrombotic therapy has not already been interrupted, the investigator should again strongly consider interrupting the anti-thrombotic therapy. In addition, for platelets < 20,000/μL, lenalidomide should be interrupted and CBC should be followed every 7 days. Appropriate interventions (i.e., platelet infusion) should be considered where applicable.

Infection

Prophylactic antibiotics should be considered in subjects 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.

Data Monitoring Committee

An independent external Data Monitoring Committee (DMC) will review safety and efficacy data collected during the conduct of the study. DMC Meetings will occur approximately every 3 months during enrollment (with the first meeting occurring when ~18 subjects have completed their first cycle of treatment) and twice per year thereafter. In addition, safety data will be reviewed in an ongoing manner to assess benefit-to-risk considerations; accrual will be stopped to a treatment arm if unacceptable toxicities are observed in that treatment arm.

Response Adjudication Committee

An independent Response Adjudication Committee (RAC) will perform a blinded, independent assessment of response (including the development of PD) prior to database lock. The RAC adjudicated response data will be used in the efficacy analysis for the study.

Number of planned subjects

Approximately 105 subjects

Study Population

Key Inclusion Criteria

- Must understand and voluntarily sign an informed consent form
- Age ≥ 18 years at the time of signing the informed consent form
- Must be able to adhere to the study visit schedule and other protocol requirements

Must have a documented diagnosis of B-cell CLL [iwCLL guidelines for diagnosis and treatment of CLL (Hallek, 2008)] meeting at least one of the following criteria:

- Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia
- Massive (i.e., > 6 cm below the left costal margin) or progressive or symptomatic splenomegaly

  - Massive nodes (i.e., > 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy
  -
  - A minimum of any one of the following disease-related symptoms must be present:
    - Unintentional weight loss ≥ 10% within the previous 6 months
    - Significant fatigue (i.e., ECOG PS 2; cannot work or unable to perform usual activities)
    - Fevers of greater than 100.5° F or 38.0° C for 2 or more weeks without other evidence of infection
    - Night sweats for more than 1 month without evidence of infection
  - Must be relapsed or refractory to at least 1 prior regimen for treatment of CLL [relapsed / refractory as defined per the iwCLL guidelines for diagnosis and treatment of CLL (Hallek, 2008)]. At least one of the prior treatments must have included a purine-analog or bendamustine based treatment regimen
  - Relapsed is defined as a subject who has previously achieved the criteria of a complete remission (CR) or partial remission (PR), but after a period of ≥6 months, demonstrates evidence of disease progression
  - Refractory is defined as treatment failure [e.g. Stable disease (SD), non response, or progressive disease] or disease progression within 6 months to the last antileukemic therapy
- Must have an Eastern Cooperative Oncology Group (ECOG) performance status score of ≤2.
- Females of childbearing potential (FCBP) must:
  - Have a negative medically supervised pregnancy test prior to starting study drug. She must agree to ongoing pregnancy testing during study therapy and after discontinuation of study drug as specified in Appendix 21.9. This applies even if the subject practices complete and continued sexual abstinence.
  - Either commit to continued abstinence from heterosexual intercourse (which must be reviewed on a monthly basis) or agree to use, and be able to comply with, effective contraception without interruption, prior to starting study drug, during study drug therapy, and after discontinuation of study drug as specified in Appendix 21.9.
- Male subjects must:
  - Agree to use a condom during sexual contact with a FCBP, even if they have had a vasectomy, during study drug therapy and after discontinuation of study drug as specified in Appendix 21.9.

  - Agree to not donate semen or sperm during study drug therapy and after discontinuation of study drug as specified in Appendix 21.9.
- All subjects must:
  - Have an understanding that the study drug could have a potential teratogenic risk
  - Agree to abstain from donating blood during study drug therapy and after discontinuation of study drug as specified in Appendix 21.9.
  - Agree not to share study drug with another person
  - Be counseled about pregnancy precautions and risks of fetal exposure as specified in Appendix 21.9.

Key Exclusion Criteria

- Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form
- Active infections requiring systemic antibiotics
- Systemic treatment for B-cell CLL within 28 days of initiation of lenalidomide treatment
- Alemtuzumab therapy within 60 days of initiating lenalidomide treatment
- Prior therapy with lenalidomide
- History of grade 4 rash due to prior thalidomide treatment
- Planned autologous or allogeneic bone marrow transplantation
- Pregnant or lactating females
- 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 initiating study drug
- 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
  - Carcinoma *in situ* of the bladder
  - Incidental histologic finding of prostate cancer (TNM stage of T1a or T1b)
- History of renal failure requiring dialysis

- Known Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV) and/or Hepatitis C Virus (HCV) infection
- Evidence of TLS per the Cairo-Bishop definition of laboratory TLS (subjects may be enrolled upon correction of electrolyte abnormalities)
- Any of the following laboratory abnormalities:
  - Calculated (method of Cockroft-Gault) creatinine clearance of <60 mL/min (creatinine clearance may also be obtained by the 24-hour collection method at the investigator's discretion)
  - 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 > 1.5 x ULN
- Uncontrolled hyperthyroidism or hypothyroidism
- Venous thromboembolism within 12 months
- ≥ Grade-2 neuropathy
- Uncontrolled autoimmune hemolytic anemia or thrombocytopenia
- Disease transformation [i.e. Richter's Syndrome (lymphomas) or prolymphocytic leukemia]
- Participation in any clinical study or having taken any investigational therapy within 28 days prior to initiating lenalidomide therapy
- Known presence of alcohol and/or drug abuse

Investigational product, dosage and mode of administration:

Celgene Corporation will supply lenalidomide 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg and 25 mg capsules for oral administration. Subjects will receive 28 days of lenalidomide per cycle.

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

Assessments

Efficacy

- Physical Exam (lymph nodes, spleen and liver measurement)
- Complete blood count (CBC) and differential
- Immunophenotyping of peripheral blood lymphocytes
- Histopathology (bone marrow aspirate/biopsy)
- Assessment for MRD by flow cytometry (peripheral blood and bone marrow

aspirate)

- Computed tomography (CT) scans
- ECOG Performance Status
- Assessment of constitutional symptoms (weight loss, fever, night sweats, fatigue)

Safety

- Vital signs
- Clinical laboratory evaluations
- Pregnancy testing
- Electrocardiogram (ECG)
- Concomitant medications
- AEs by NCI CTCAE Version 3.0, with modifications recommended by the iwCLL guidelines for the diagnosis and treatment of CLL (Hallek, 2008), and by the Cairo-Bishop grading system for TLS
- 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. Subjects will be followed until 80% of the subjects have progressed or died or up to five years after the last subject was randomized, whichever occurs later.

Exploratory

- FISH analyses, V_H mutational status assessment, TP53 mutation, , ZAP-70 expression by flow cytometry
-
- Beta-2 Microglobulin (β2M)
- Plasma PK (in up to 40 subjects who provide consent at select centers)
-
- Quality of Life as measured by FACT-Leu questionnaire and EQ-5D

Statistical Analysis

Overview

This study will be conducted using a randomized Bayesian schedule-administration design that jointly models toxicity/disease progression outcomes using an extension method. The object of interest is to determine if a particular treatment administration schedule is superior to other competing schedules.

The approximate sample size will be 105 subjects, 35 per arm, barring early stopping.

Operationally the study will proceed as follows: Subjects will be randomized to one of the three treatment arms. The first interim analysis (toxicity only) will be performed once 18 subjects complete one 28-day cycle.

Subsequent interim analyses will occur at 13-week intervals to monitor both combined toxicity and disease progression. Depending on the calculated posterior probability of toxicity and disease progression, any one of the three treatment arms may be dropped for excessive toxicity or progression rate.

Safety Analysis

All subjects who receive at least 1 dose of study drug will be included in the safety analyses. AEs, vital sign measurements, clinical laboratory information, and concomitant medications will be tabulated and summarized for each treatment arm during therapy. 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 MedDRA terms and by NCI CTCAE Version 3.0, with modifications recommended by the iwCLL guidelines for the diagnosis and treatment of CLL (Hallek, 2008), and by the Cairo-Bishop grading system for TLS. Time to first dose reduction will be summarized for each regimen.

Death and clinically important AEs (including TFR, TLS, 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.

Efficacy Analysis

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

Response, duration of response, TTR, TTP, EFS, PFS, and OS will be summarized. The Kaplan-Meier procedure will be used to characterize the time-to-event curves in these analyses when there is censoring.

Exploratory Analysis

Pharmacokinetics Analysis

If the data are sufficient, noncompartmental PK parameters, such as T_{max}, C_{max}, AUC, CL/F, and $t_{1/2}$, will be estimated. Descriptive statistics will be provided for plasma concentrations and PK parameters. Lenalidomide concentration data obtained from all visits may be used to develop the population PK model. The relationship between pharmacokinetics and response (biomarkers or clinical outcomes as appropriate) will be explored.

Analysis and Reporting

In addition to the interim analyses focusing on toxicities and disease progression, efficacy analyses will be performed when 80% of the subjects have progressed or died, or five years after the last subject was randomized, whichever occurs later.

Figure 1: Overall Study Schema

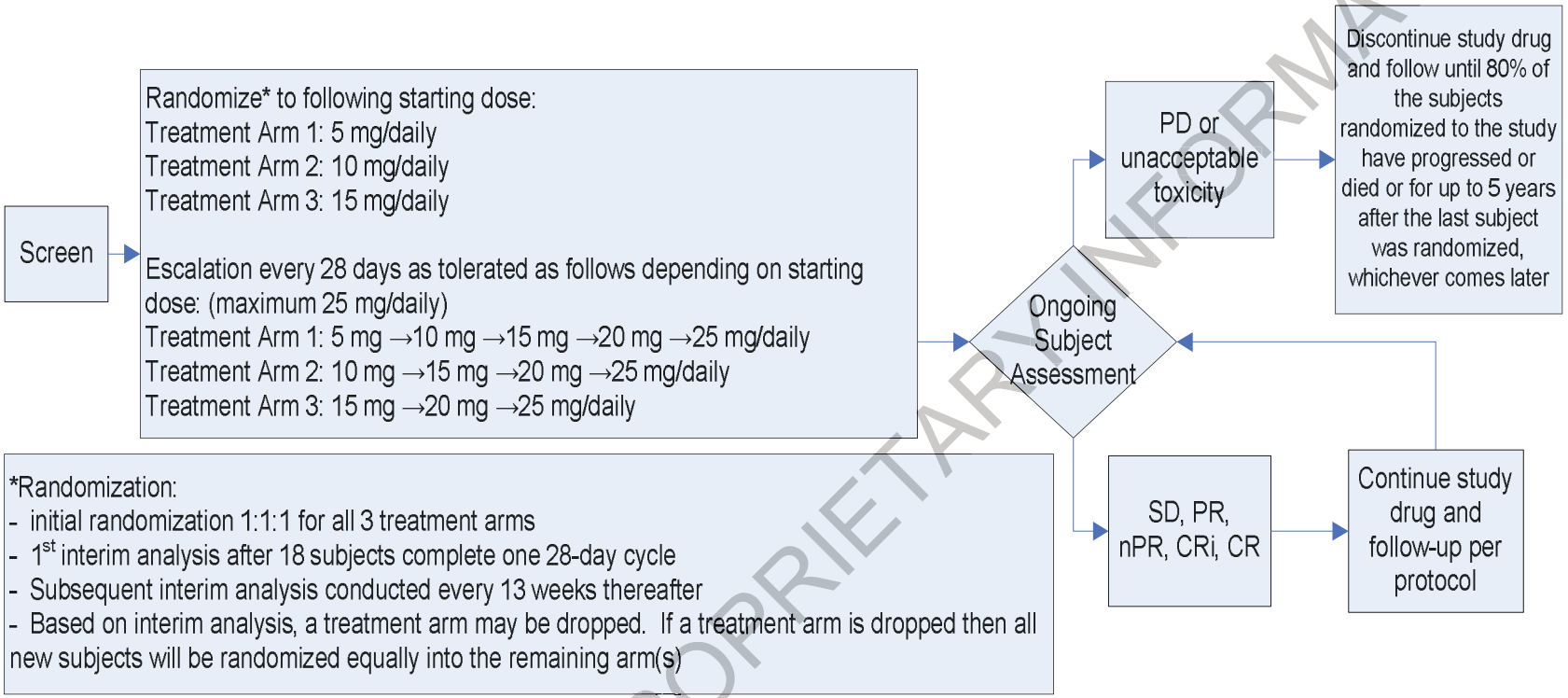

Table 2: Schedule of Assessments

Procedure[a]	Screening ≤28 days prior to Day 1	Study Day 1	Days 2 and 4 for Cycle 1 and the first cycle at Dose Level +1,+2,+3,+4 +/- 1 day	Days 8, 15, 22 of Cycle 1 and first cycle at Dose Level +1, +2,+3, +4 Days 8 and 15 of Cycle 2 +/- 2 days	Every 28 days (4 wks)[b, c] (1st day of each cycle)	At time of clinical manifestation of TFR	At time of clinical resolution of TFR	CR/CRi/ PR confirmation visit	Treatment discontinuation[c]	Every 12 weeks (+/- 7 days) until study closure
ICF/Inclusion/Exclusion	X	--	--	--	--	--	--	--	--	--
Clinical staging for CLL (Rai or Binet classification)	X	--	--	--	--	--	--	--	--	--
Medical history	X	--	--	--	--	--	--	--	--	--
Pregnancy test[d]	X[d]	X[d]	--	--	X[d]	--	--	--	X[d]	--
Pregnancy and risk counseling	X[e]	X[e]	--	--	X[e]	--	--	--	X[e]	--
ECOG Performance Status	X	X	--	--	X	--	--	--	X	--
Evaluation of constitutional symptoms	X	X	--	--	X	--	--	--	X	--
Physical examination to assess lymph nodes, spleen and liver[f]	X	X	--	--	X	--	--	--	X	--
Vital signs including weight, height (at screening only)[g]	X	X	X	X	X	--	--	--	X	--
CT scans[h]	X	--	--	--	--	--	--	X[h]	X[h]	--
ECG (12 lead)[i]	X	--	--	--	X (starting at C3D1 then every 84 days thereafter)	--	--	--	X	--
TLS monitoring and prophylaxis and TFR monitoring[j]	X	X	X	X	X	--	--	--	--	--

Table 2: Schedule of Assessments (Continued)

Procedure[a]	Screening ≤28 days prior to Day 1	Study Day 1	Days 2 and 4 for Cycle 1 and the first cycle at Dose Level +1,+2,+3,+4 +/- 1 day	Days 8, 15, 22 of Cycle 1 and first cycle at Dose Level +1, +2,+3, +4 Days 8 and 15 of Cycle 2 +/- 2 days	Every 28 days (4 wks)[b, c] (1st day of each cycle)	At time of clinical manifestation of TFR	At time of clinical resolution of TFR	CR/CRi/ PR confirmation visit	Treatment discontinuation[c]	Every 12 weeks (+/- 7 days) until study closure
Hematology[k]	X	X	X	X	X	--	--	--	X	--
Chemistry[l]	X	X	X	X	X	--	--	--	X	--
Urinalysis[m]	X	X	X	X	X	--	--	--	X	--
Calculated (method of Cockroft-Gault) creatinine clearance (24-hour collection method may also be used at the investigator's discretion)[l]	X	--	--	--	--	--	--	--	--	--
Direct antiglobulin (DAT) test[n]	X	--	--	--	--	--	--	--	--	--
Thyroid function test[o]	X	--	--	--	X (starting at C3D1 then every 84 thereafter)	--	--	--	X	--
Bone marrow aspirate, biopsy, peripheral blood slides[p]	X[p]	X[p]	--	--	--	--	--	X[p] (CR/CRi only)	--	--
Disease diagnosis confirmation)[q]	--	X	--	--	--	--	--	--	--	--
MRD evaluation[r]	--	--	--	--	--	--	--	X[r] (CR/CRi only)	--	--

Table 2: Schedule of Assessments (Continued)

Procedure[a]	Screening ≤28 days prior to Day 1	Study Day 1	Days 2 and 4 for Cycle 1 and the first cycle at Dose Level +1,+2,+3,+4 +/- 1 day	Days 8, 15, 22 of Cycle 1 and first cycle at Dose Level +1, +2,+3, +4 Days 8 and 15 of Cycle 2 +/- 2 days	Every 28 days (4 wks)[b, c] (1st day of each cycle)	At time of clinical manifestation of TFR	At time of clinical resolution of TFR	CR/CRi/ PR confirmation visit	Treatment discontinuation[c]	Every 12 weeks (+/- 7 days) until study closure
FACT-Leu and EQ-5D questionnaire	--	X	--	--	X (starting at C3D1 then every 56 days thereafter)	--	--	--	X	--
Study drug administration[s]	--	X	--	--	X	--	--	--	X	--
Adverse events[t]	X	X	X	X	X	--	--	--	X	--
Assessment of Second Primary Malignancy[u]	X	X	X	X	X	--	--	--	X	X
Concomitant medication/therapies[w]	X	X	X	X	X	--	--	--	X	X
Assessment of response[v]	--	--	--	--	X[u]	--	--	--	X	--
Survival[w]	--	--	--	--	--	--	--	--	--	X
Beta-2 Microglobulin (β2M)[x]	--	X	--	--	--	--	--	--	--	--
ZAP-70 expression[y]	--	X	--	--	--	--	--	--	--	--
V_H mutational status/ TP53 mutation[y]	--	X	--	--	--	--	--	--	--	--
Cytogenetic analysis (FISH)[y]	--	X	--	--	--	--	--	--	--	--

a. All study procedures should be performed within ± 3 days of the scheduled visit unless otherwise stated.
b. These assessments must be performed every 28 days (±3days). If a Day 1 for any cycle is delayed, an unscheduled visit should be performed, if required, to ensure these assessments are performed at least every 28 days (±3days) during the study.

c. For those subjects who discontinue study drug for reasons other than disease progression or withdrawal of consent, study visits should continue every 28 days to assess response until documentation of disease progression or until a new CLL therapeutic regimen is started, whichever comes first. During these visits for these subjects only the following assessments are required: hematology, ECOG performance status, evaluation of constitutional symptoms, physical exam for liver, spleen and lymph nodes, adverse events, assessment for second primary malignancies, concomitant medications/therapies and assessment of response.
d. Females of childbearing potential (FCBP) must have a medically supervised pregnancy test (serum or urine with sensitivity of at least 25 mIU/mL) per the frequency specified in Appendix 21.9 Pregnancy Prevention Risk Minimization Plans
e. All male and FCBP subjects must be counseled about pregnancy precautions and risks of fetal exposure as detailed in Appendix 21.9 Pregnancy Prevention Risk Minimization Plans.
f. Physical examination of the lymph nodes, spleen and liver will be performed at screening, Study Day 1 and every 28 days thereafter and at the treatment discontinuation visit. Lymph node evaluation will record the bi-dimensional diameter of the largest palpable nodes in each of the following sites: cervical, axillary, supraclavicular, inguinal and femoral. The size of the liver and spleen will be assessed by palpation and recorded.
g. Vital signs include: temperature, pulse, blood pressure, weight and height (height to be measured during screening only).
h. CT scans of the neck, chest, abdomen and pelvis to assess lymphadenopathies will be performed during screening and at the PR and CR/CRi confirmation visits (≥8 weeks - ≤ 12 weeks after all clinical and laboratory response criteria have been met for PR or CR/CRi) and for all subjects, except those who discontinue due to PDs, at the treatment discontinuation visit. At screening, if medically justified, the possibility of not repeating the CT Scan when previously performed within 56 days of randomization will be evaluated by the Celgene Medical Monitor on a case by case basis. Those subjects whose response was down-graded based on the CT scan interpretation at the PR or CR/CRi confirmation visit will have the CT scan repeated 4 months later at the location where remaining disease has been documented as long as clinical and laboratory response remains present to try to document further improvement..
i. ECG will be performed and interpreted locally. After the screening ECG, the next ECG will be done at Cycle 3 Day 1, and then every 12 weeks while on study drug, and at treatment discontinuation.
j. TLS prophylaxis, comprising of oral hydration and allopurinol 300 mg/day will be initiated at least 3 days prior to starting study drug and for a minimum of the first 3 treatment cycles. For subjects with known allergy to allopurinol prior to study initiation or for those who develop an allergy during the course of study therapy, the medical monitor should be contacted. To maintain fluid intake, subjects should be instructed to drink 8-10 eight ounce glasses of water each day for the first 14 days of each cycle during the dose escalation period. 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.
k. Hematology: Local lab assessments include HGB, ANC, ALC and platelet count. At screening, subject must meet eligibility criteria based on central lab results. At Study Day 1, subject must meet eligibility criteria based on local or central lab results prior to initiating study therapy
l. Chemistry: Local lab assessments include potassium, calcium, phosphorus, creatinine, total bilirubin, AST/SGOT, ALT/SGPT, and uric acid. At screening, subject must meet eligibility criteria based on central lab results. At Study Day 1, subject must meet eligibility criteria based on local or central lab results prior to initiating study therapy, however, a re-calculation of creatinine clearance is not required at Study Day 1.
m. Urinalysis: Local laboratory assessments will include ketones, sediments and specific gravity.
n. DAT (direct antiglobulin test) will be performed at screening and analyzed at the central laboratory. The DAT test should be repeated if the investigator suspects hemolytic anemia during the course of the study. Analysis of DAT will be completed by local laboratory as part of this amendment, protocol amendment #6.
o. TSH (thyroid-stimulating hormone), free T3, and free T4 levels will be assessed at screening, Cycle 3 Day 1 and every 12 weeks while on study drug and at treatment discontinuation. All samples will be analyzed centrally. Collection of TSH samples is discontinued as of this amendment, protocol amendment #6.
p. A peripheral blood, bone marrow aspirate and bone marrow biopsy slide will be prepared and submitted to the central pathology reviewer for all subjects during screening or at cycle 1 day 1and at the CR/CRi confirmation visit. At screening, if medically justified, the possibility of not repeating the bone marrow aspirate/biopsy when previously performed within 56 days of randomization will be evaluated by the Celgene Medical Monitor on a case by case

basis if sufficient and appropriate samples are available for submission to the central pathology reviewer. For those subjects who reach CR or CRi, a peripheral blood, bone marrow aspirate and bone marrow biopsy slide will be prepared and submitted to the local pathology reviewer at the CR/CRi confirmation visit (≥ 8 weeks - ≤ 12 weeks after all clinical and laboratory response criteria have been met). If the bone marrow is hypocellular, a repeat specimen should be obtained after 4 weeks, provided that the blood counts have recovered. If the bone marrow biopsy shows disease involvement (30% or greater lymphocytes, or nodules positive for B-CLL cells by immunohistochemistry), an additional bone marrow biopsy and aspirate will be taken 4 months later as long as clinical and laboratory response remain to document further improvement. All bone marrow and aspirate samples will also be analyzed locally and this data will be captured on the eCRFs.

q. Peripheral blood for disease diagnosis confirmation (by immunophenotyping as per Hallek, 2008) will be drawn at Study Day 1 for all subjects. All samples will be analyzed centrally.

r. **Initial MRD assessment:** MRD status will be evaluated for those subjects who reach CR or CRi. A peripheral blood and bone marrow aspirate sample will be collected for MRD analysis by flow cytometry at the CR/CRi confirmation visit (≥8 weeks - ≤ 12 weeks after all clinical and laboratory response criteria have been met for CR/CRi). If peripheral blood and bone marrow are both MRD-positive, peripheral blood samples will be repeated and assessed up to 3 additional times at 8 week intervals to try to document MRD negativity in subjects who reach confirmed CR or CRi (see Follow-up MRD assessments). If peripheral blood is MRD-negative and bone marrow is MRD-positive, both peripheral blood and bone marrow should be retested for MRD negativity after ≥ 12 weeks. If this repeat bone marrow is MRD-positive, no further testing for MRD will be performed. If both the peripheral blood and bone marrow are MRD-negative, peripheral blood will be tested every 6 months for assessment of MRD until subject discontinues study drug. All samples will be analyzed locally. **Follow-up MRD assessments**: If any of the repeat peripheral blood assessments indicate MRD-negativity, a bone marrow aspirate sample should be collected and retested as soon as possible to confirm MRD negativity. If the bone marrow is MRD-positive, both peripheral blood and bone marrow should be retested for MRD negativity after ≥ 12 weeks. If this repeat bone marrow is MRD-positive, no further testing for MRD will be performed. If at any time, the bone marrow is MRD-negative, peripheral blood will be tested every 6 months for assessment of MRD until subject discontinues study drug. All samples will be analyzed locally.

s. Study drug to be dispensed at Day 1 of each cycle. Subjects should be instructed to return the study drug at Day 1 of each 28-day cycle. No more than a 28-day supply of study drug will be dispensed at a time.

t. AEs will be reported from the time informed consent is signed to 30 days post last dose of study drug. AEs that lead to study discontinuation should be followed until resolution or stabilization. For subjects who discontinue study treatment but continue to be followed every 28 days until PD or new CLL therapy, AEs will be reported until 30 days post last dose of study drug or until study discontinuation, whichever occurs last. SAEs will be reported from time informed consent form is signed to 30 days post last dose of study drug. SAEs will be reported at any time post last dose of study drug if it is considered related to study drug.

u. Second primary malignancies will be monitored as events of interest and must be reported as serious adverse events regardless of the treatment arm the subject is in. 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 80% of the subjects have progressed or died or up to five years after the last subject was randomized, whichever occurs later. 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 (e.g., any confirmatory histology or cytology results, X-rays, CT scans, etc.).

v. Investigators to provide assessment of CR, CRi, nPR, PR, SD, and PD based on laboratory, physical exam, assessment of constitutional symptoms and if appropriate CT scan findings (CT scans are to be performed at baseline and to confirm PR or CR/CRi). For confirmed PR, nPR or CR/CRi, response must be maintained for ≥ 8 weeks as per the iwCLL guidelines for the diagnosis and treatment of CLL (Hallek, 2008) Tumor response will be assessed according to

the iwCLL guidelines (Hallek, 2008) for the diagnosis and treatment of CLL (Hallek, 2008), including CR, CRi, nPR, PR, SD, and PD. Evaluation of response will be performed after 3 cycles of therapy and every 4 weeks thereafter.

w. Subjects who develop PD or disease transformation [Richter's syndrome (lymphomas) or prolymphocytic leukaemia], at any time, or who choose to discontinue study participation for any reason, or who begin a new CLL therapeutic regimen will be discontinued from the study and will be followed for survival, assessment for second primary malignancies and subsequent CLL therapies until 80% of the subjects have progressed or died or up to five years after the last subject was randomized, whichever occurs later.

x. Blood samples for β2M will be collected at baseline. All Samples will be analyzed centrally.

y. Blood samples for ZAP-70, V_H mutational status / TP53 mutation analysis and FISH studies for cytogenetic assessment (CCND1/IgH fusion, 11q, 17 p, 13 q, and Trisomy 12) will be collected at Study Day 1 pre-dose. All samples will be analyzed centrally.

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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
ANOVA/ANCOVA	Analysis of Variance/Covariance
AST (SGOT)	Asparate transaminase (serum glutamic oxaloacetic transaminase)
ATC	Anatomic Therapeutic Chemical
β2M	Beta-2 Microglobulin
β-HCG	Beta-human chorionic gonadotropin hormone
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Confidence Interval
CrCl	Creatinine Clearance
CLL	Chronic lymphocytic leukemia
CMV	Cytomegalovirus
CNS	Central nervous system
CR	Complete response
CRi	Complete response with incomplete bone marrow recovery
eCRF	Electronic case report form
CR MRD+	Complete response – Minimal residual disease positive
CR MRD-	Complete response – Minimal residual disease negative
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events

Table 3: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
DAT	Direct Antiglobulin Test
DCF	Data Clarification Form
DLT	Dose-limiting toxicity
DMC	Data Monitoring Committee
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EE	Efficacy Evaluable Population
EFS	Event-free survival
EMA	European Medicines Agency
EQ-5D	EuroQol
F	Fludarabine
FACT-Leu	Functional Assessment of Cancer Therapy-Leukemia
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
FISH	Fluorescence in Situ Hybridization
FNA	Fine Needle Aspirate
GCP	Good Clinical Practice
GCSF	Granulocyte colony-stimulating factor
HGB	Hemoglobin
HCT	Hematocrit
HIV	Human immunodeficiency virus
HRQL	Human Related Quality of Life
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
V_H	Immunoglobulin Heavy-chain Variable-region
IL-6	Interleukin 6

Table 3: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
IMiD	Immunomodulatory drug
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent to Treat
IV	Intravenous
IVRS	Interactive Voice Response System
iwCLL	International Workshop on CLL
LDH	Lactate dehydrogenase
LN	Lymph node
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Minimal residual disease
MTD	Maximum-tolerated dose
MTDEL	Maximum tolerated dose escalation level
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCI-WG	National Cancer Institute Working Group criteria for chronic lymphocytic leukemia
NK cells	Natural killer cells
NOS	Not otherwise specified
NSAID	Non-steroidal anti-inflammatory drug
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive disease
PFS	Progression free survival
PK	Pharmacokinetic

Table 3: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
PR	Partial Response
PS	Performance Status
RAC	Response Adjudication Committee
RBC	Red blood cell
RIC	Reduced intensity conditioning
SAE	Serious adverse event
SC	Subcutaneous
SCID	severe combined immunodeficiency
SCT	Stem cell transplantation
SD	Stable disease
SGOT	Serum-Glutamic-Oxaloacetic Transaminase
SLL	Small Lymphocytic Lymphoma
SOP	Standard Operating Procedure
TFR	Tumor Flare Reaction
TLS	Tumor Lysis Syndrome
TNF-α	Tumor necrosis factor alpha
TNM	Tumor-nodes-metastasis
TP53	Tumor protein 53
TSH	Thyroid stimulating hormone
TTE	Time to event
TTF	Time to treatment failure
TTP	Time to progression
TTR	Time to response
VEGF	Vascular Endothelial Growth Factor

5. INTRODUCTION

5.1. Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia is the most prevalent adult leukemia among Caucasians. It affects mainly elderly individuals with the median age at presentation of 72 years, but up to one third of newly diagnosed patients are under the age of 65 years (Leukemia and Lymphoma Society, 2008). It is an incurable lymphoproliferative malignancy manifested by progressive accumulation of morphologically mature but functionally incompetent lymphocytes in the blood, bone marrow, and lymphoid tissues. The clinical course of CLL ranges from indolent disease (Rai 0, Binet A) with long-term survival over 12 years to aggressive disease (Rai III/IV, Binet C) with median survival of 2 years (Montserrat, 1995).

Multiple, randomized, Phase 3 studies have attempted to identify treatments that improve overall survival (OS). Chlorambucil, approved by the FDA in March 1957, is a well-tolerated oral agent that can induce partial remissions (PR) in advanced stage CLL patients and has been in use for many decades. In early stage CLL patients, the French Co-operative group on CLL (Dighiero, 1998) reported that early therapy with alkylator-based therapy did not improve survival compared to observation alone. Due to the availability of newer treatment options demonstrating improved efficacy, chlorambucil is not considered the optimal first-line treatment choice by physicians in the United States. However, the drug is still considered a valid treatment option for elderly patients and those with comorbidities that preclude treatment with more aggressive treatment regimens.

Fludarabine is approved by the FDA (April 1991) as a second-line agent. Clinical studies of fludarabine have shown superior overall response rates, complete response rates, and progression free survival, but no improvement in overall survival was noted (Rai, 2000) (Catovsky, 2007) In recent years, data from several phase 2/3 clinical studies in which fludarabine was combined with cyclophosphamide and/or rituximab demonstrated high response rates and long progression-free survivals, with increased toxicity compared to chlorambucil, but as yet have not shown a survival benefit (O'Brien, 2001) (Byrd, 2003) (Wierda, 2005) (Eichhorst, 2006) (Tam, 2007).

In September 2007, alemtuzumab was also approved as first line therapy of B-cell CLL. In an open-label, randomized (1:1) study of 297 patients, the patients receiving alemtuzumab experienced longer PFS compared to those randomized to receive chlorambucil (median PFS 14.6 months vs. 11.7 months respectively). The overall response rates (ORR) were 83% and 55% ($p < 0.0001$) and the CR rates were 24% and 2% ($p < 0.0001$) (Hillmen, 2007).

In March 2008, bendamustine was approved for the treatment of patients with chronic lymphocytic leukemia. The labeling states "Efficacy relative to first line therapies other than chlorambucil has not been established". The study comparing bendamustine, 100 mg/m^2 IV on days 1 and 2 every 28 days, to chlorambucil, 0.8 mg/kg/day orally on days 1 and 15 every 28 days, was conducted in 301 patients (153 on bendamustine and 148 on chlorambucil) with Binet stage B or C (Rai stages I-IV) requiring treatment. The ORR was 59% for bendamustine vs 26% for chlorambucil ($p < 0.0001$) with 8% vs <1% CRs for bendamustine and chlorambucil arms, respectively. The median PFS was 18 months for bendamustine vs 6 months for chlorambucil ($p < 0.0001$) (TREANDA package insert, 2008). Since receiving FDA approval in 2008, market

research data demonstrate increased bendamustine usage in first line and in the relapsed/refractory setting either as a single-agent or in combination with rituximab.

Based on these data and the indolent clinical course of many CLL patients, the current medical practice for most early stage CLL patients is that of "watchful waiting." For those CLL patients with advanced stage disease who require treatment, initial treatment selection is largely based on age, performance status and co-morbid conditions and is either chlorambucil monotherapy, fludarabine-based or bendamustine-based combination regimens.

Many CLL patients relapse after initial therapy. Second-line treatment and subsequent treatments often consist of purine-analog-based treatment regimens. Eighty-five percent of patients previously responsive to fludarabine respond to re-treatment with the same agent but the response rate falls to 12% in patients who were refractory to previous fludarabine therapy when re-treated with fludarabine single agent (Thomas, 1998), and between 39% to 58% in patients re-treated with fludarabine combined therapy (fludarabine with cyclophosphamide, or cyclophosphamide and rituximab) (O'Brien, 2001) (Wierda, 2005). Patients who become refractory or resistant to purine analogues containing regimens have a poor prognosis and limited therapeutic options.

On 07 May 2007, alemtuzumab was initially approved for patients previously treated with alkylating agents and refractory to fludarabine. In a study of 93 heavily pretreated fludarabine refractory patients a response rate of 33% (2% CR) was achieved, with the median time to progression for responders of 9.5 months and a median overall survival of 16 months for all patients and 32 months for responders (Keating, 2002). Subjects in this study with at least one lymph node > 5 cm (bulky lymphadenopathy) achieved a 12% PR and 0% CR. Toxicity with alemtuzumab therapy was not negligible and included infusion-related toxicity (81%), immunosuppression, and infections (55%) with reactivation of cytomegalovirus seen in 7 patients.

On 19 September 2007, alemtuzumab's accelerated approval was converted to a full approval with a revised indication, "as a single agent for the treatment of B-cell chronic lymphocytic leukemia (B-CLL)". In an open-label, randomized (1:1) study of 297 patients, the patients who received alemtuzumab experienced longer PFS compared to those randomized to receive chlorambucil (median PFS 14.6 months vs. 11.7 months, respectively). The ORRs were 83% and 55% ($p < 0.0001$), and the CR rates were 24% and 2% ($p < 0.0001$). Despite the approval, use of alemtuzumab as a treatment for previously untreated patients remains very limited.

Although alemtuzumab has demonstrated efficacy in the fludarabine-refractory CLL population, several studies have shown that patients that have CLL bulky disease (i.e lymphadenopathy greater than 5 cm) are poor responders to alemtuzumab therapy (Keating, 2002) (Fiegl, 2006) (Osterborg, 1997). A recent historical review by Tam et al (Tam, 2007) underlines that fludarabine refractory CLL patients who have bulky lymphadenopathy constitute a high unmet medical need despite the availability of new salvage therapy in the last decades which include purine analogues combinations and monocloncal antibodies.

On 26 October 2009 the U.S. Food and Drug Administration granted accelerated approval to ofatumumab (Arzerra™) for the treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab. The approval was based on a clinically meaningful and durable overall response rate (ORR) observed in a single-arm, multicenter trial in 154

patients with relapsed or refractory CLL. Accelerated approval was based on the results of a pre-specified subgroup of 59 patients who were refractory to both fludarabine and alemtuzumab. Drug refractoriness was defined as failure to achieve at least a partial response to, or disease progression within 6 months of the last dose of fludarabine or alemtuzumab. The primary efficacy outcome was durable ORR as determined by the 1996 National Cancer Institute Working Group (NCIWG) Guidelines for CLL.

5.2. Lenalidomide

Lenalidomide (REVLIMID®; Celgene Corp., NJ, USA) is a member of a class of pharmaceutical compounds known as immunomodulatory drugs (IMiDs®). It offers potential benefit over the first commercially available IMiD, thalidomide, in terms of both safety and efficacy in human subjects (Galustian, 2004) (Tohnya, 2004). The key to its therapeutic potential lies in the fact that it has multiple mechanisms of action, which act to produce both anti-inflammatory and anti-tumor effects. These effects are thought to be contextual in that they depend on both the cell type and the triggering stimulus. To date, lenalidomide has been associated with TNF-α inhibitory, T cell costimulatory, and antiangiogenic activities (Galustian, 2004).

REVLIMID® has been approved by multiple global Health Authorities (including the FDA, but excluding the EU) for the treatment of patients with transfusion dependent anemia due to Low- or Intermediate-1-risk myelodysplastic syndrome associated with a deletion 5q cytogenetics abnormality with or without other cytogenetic abnormalities.

REVLIMID® has also been approved by multiple global Health Authorities (notably including the US and EU) in combination with dexamethasone, for patients with previously treated multiple myeloma.

Lenalidomide is being investigated as treatment for various oncologic indications, including multiple myeloma, non-Hodgkin's lymphomas, and solid tumors. It is also being explored as a treatment for inflammatory conditions. While many of the studies are ongoing, results from controlled and uncontrolled studies in subjects with MDS and MM are available.

5.3. Background and rationale for lenalidomide in chronic lymphocytic leukemia

5.3.1. Background

The cellular interplay between the microenvironment and the malignant CLL clone and the decreased sensitivity of B-CLL cells to apoptotic signal is thought to play an important role in the pathophysiology and development of CLL disease (Ghia, 2005). CLL cells can secrete various prosurvival cytokines (TNF-α, IL-6 and VEGF) and modulate their receptor expression in a paracrine/autocrine growth loop manner (Hoffbrand, 1993).

Lenalidomide has been reported to inhibit TNF-α production, modulate cytokine production and also to have immunomodulatory properties that are thought to be critical for the activity of this drug in chronic lymphocytic leukemia (Corral, 1996) (Corral, 1999). Lenalidomide co-stimulates T-cells and enhances antitumor immunity, which is mediated by T-helper-1 type cytokines, such as interferon-γ and interleukin-2 (IL-2); it also enhances other innate immune

cells such as natural killer cells, which can increase tumor cell death (Bartlett, 2004) (Hayashi, 2005).

Additional experiments performed in vitro confirmed the ability of lenalidomide to increase NK-cell mediated killing of primary B-CLL tumor cells in both a PBMC co-culture model and NK mediated antibody-dependent cellular cytotoxicity (ADCC) model (Wu, 2008)(Lapalombella, 2008). Co-treatment of B-CLL cells and NK cells with lenalidomide was shown to enhance rituximab-mediated ADCC in vitro, however a greater enhancement was observed when B-CLL cells were not pre-treated with lenalidomide suggesting that alternative sequencing strategies might be also beneficial when combining the two drugs in a clinical setting (Lapalombella, 2008). Interestingly, lenalidomide also synergized with rituximab to promote animal survival in a severe combined immunodeficiency (SCID) mouse-disseminated lymphoma xenograph model. Lenalidomide treatment enhanced rituximab's NK cell antitumor activity, and resulted in the in vivo expansion of murine NK cells, suggesting a role for the co-stimulatory properties of this agent in this model (Hernandez- Ilizaliturri, 2005).

The potential ability of lenalidomide to enhance immune cell recognition in CLL was also reported in a recent work by Ramsay et al. (Ramsay, 2008) demonstrating that lenalidomide can modulate the actin cytoskeleton and improve the defect in B-CLL cells and T-cells immune synapse formation and function.

Additional work is underway to better elucidate lenalidomide's mechanism of action in CLL and its ability to modulate the cellular interplay between the microenvironment and the malignant CLL clone.

5.3.2. Clinical studies

5.3.2.1. Relapsed/refractory CLL

Initial clinical studies were conducted with thalidomide, a less potent immune modulator than lenalidomide also capable of inhibiting TNF-α, that has known anti-angiogenic properties. Thalidomide was studied in combination with fludarabine in previously untreated CLL (Chanan-Khan, 2005). Although this study investigated the efficacy and safety of the combination regimen of fludarabine and thalidomide, the design of the study called for the administration of thalidomide alone for the first 7 days of therapy, after which fludarabine was added. Antitumor effects, manifested as reduction on the peripheral blood lymphocyte count, occurred within 7 days of starting thalidomide, prior to institution of fludarabine, suggesting that thalidomide alone has anti-CLL activity.

Based on the observations made with thalidomide, single-agent lenalidomide was studied in relapsed/refractory CLL (Chanan-Khan, 2006a) (Ferrajoli, 2008). Chanan-Khan treated patients with relapsed/refractory CLL with lenalidomide (25mg x 21 d q 28 days). Patients with stable disease (SD) or better response were continued on therapy for a maximum of 12 months while those with progressive disease (PD) were to receive monthly rituximab (375mg/m2) added to lenalidomide. Forty-five patients were enrolled. Median age was 64 years (range: 47 to 75 years), and advanced Rai stage (III or IV) disease was noted in 64%. The median number of prior therapies given was three (range: 1 to 10 therapies), with 51% of the patients refractory to fludarabine. Using an intent-to-treat analysis, major responses were seen in 26 patients (57.7%; 95% CI, 32% to 62%) with six patients (13.3%) achieving a CR, including 5 (11%) molecular

CRs, and 20 (44.4%) achieving a PR. Antitumor activity of lenalidomide was evident as early as day 8 of treatment with 24 (70.5%) of 34 patients (34 patients who had day 1 ALC of >5000 cells/uL and day 8 ALC available) demonstrating a decrease in their peripheral blood absolute lymphocyte count (ALC). Clinical responses (CR or PR) were observed in 40% of the patients with del (11)(q23) adverse cytogenetics and in 40% of patients with bulky disease. The median PFS of all patients enrolled was 19.4 months (range 1.2-31.8) (Chanan-Khan, 2007). Fatigue (83%) and flare reaction (tender swelling of lymph nodes and/or rash) (58%) were the most common non-hematologic AEs reported. Other important AEs reported were tumor lysis syndrome (5%); Grade 3 and 4 thrombocytopenia (45%), and Grade 3 and 4 neutropenia (70%). Pulmonary embolism was reported in two patients (5%).

Ferrajoli treated patients with relapsed/refractory CLL with lenalidomide administered daily for 28 days out of 28 day cycles up to disease progression. All patients received lenalidomide at 10 mg daily for 28 days followed by titration upward by 5 mg increments every 28 days to a maximum dose of 25 mg daily. Forty-four (44) patients have been enrolled and were evaluated for response. The median daily dose of lenalidomide tolerated by the patients was 10 mg. The median age was 64 years (range: 49 to 86 years), the median number of prior treatments was 5 (range: 1 to 15), and the median β2M at entry was 4.3 mg/dL (1.6 to 10.1). Fifty nine percent of the patients carried unfavorable genomic abnormalities (17p or 11q23 deletions) and 66% had unmutated V_H. Twelve patients (27%) were refractory to fludarabine. Responses according to NCI-WG criteria assessed after 3 months of treatment based on an intent-to-treat analysis showed that 14 patients (32%) had achieved a response [3 CR (7%), 1 nodular PR (2%), 10 PR (23%)]. Time to best response was 6 months in 11 patients and 9 months in 3 patients. The median response duration has not been reached. Eleven patients (25%) had stable disease (SD) or clinical improvement and were able to continue on treatment past the third month, and 17 patients (39%) progressed and two patients died of early infectious complication. Thirty two patients (73%) are alive with a median follow up of 14 months. Myelosuppression was the most common toxicity with in the courses, 41% ≥ Grade 3 neutropenia and 16% Grade 3 thrombocytopenia. TFR was observed in 12% of the courses (Grade ≤ 2 in 10% and Grade ≥ 3 in 2%), with a greater incidence (53%) in patients with lymph nodes larger than 5 cm. Grade ≥ 3 fatigue and diarrhea were reported in 1% and 2% of the courses, respectively.

TFR was a frequent adverse event reported in both studies and was well managed with non steroidal anti-inflammatory agents (NSAIDs) and/or corticosteroids or in some case narcotic analgesics. In Chanan-Khan's study (Chanan-Khan, 2006b), out of the 45 patients treated with lenalidomide, no TFR prophylaxis was given to the first 29 patients (Group A). Subsequently, 16 patients received prophylaxis with prednisone 20 mg po qd x 5 days followed by 10 mg po qd x 5 days starting on Day 1 of treatment (Group B). The prophylaxis did not decrease the incidence of TFR (83% [Group A] vs. 81% [Group B]). TFR ≥ Grade 2 was seen in 31% of Group A and 6% of Group B. It thus appears that steroid prophylaxis decreases the severity of the reaction, but not the overall incidence. In the group of patients who developed tumor flare, 4 CRs were achieved, all in patients who had experienced ≥ Grade 2 tumor flare reaction in comparison to 19 patients with ≤ PR who had experienced a median tumor flare severity Grade 1 (Chanan-Khan, 2006a). These preliminary data seem to indicate that patients who develop a more severe flare reaction may also achieve a better remission. However, in Ferrajoli et al. study the occurrence of a tumor flare reaction did not predict for a higher response rate with an overall response of 38% and 34% in patients with and without a TFR (Ferrajoli, 2008).

Additional single-center clinical studies investigating other dose regimens in relapsed/refractory CLL are in progress.

5.3.2.2. Previously untreated symptomatic CLL

In addition, two studies were conducted in previously untreated symptomatic CLL subjects (Chen, 2008), (Ferrajoli, 2008).

Chen treated previously untreated symptomatic CLL subjects with single agent lenalidomide. The starting dose for lenalidomide was initially 10 mg daily with weekly 5mg dose escalations to the target dose of 25 mg daily x 21 days every 28 day cycle. Toxic events in the first 2 subjects (TLS requiring dialysis; neutropenic sepsis) led to a study halt with DSMB review, and subsequent protocol amendments to reduce both the starting and target doses (2.5 mg and 10 mg, respectively, days 1-21), slow the dose escalation rate (2.5 mg cycle 1, 5 mg cycle 2, 10 mg cycle 3 and thereon), extend allopurinol TLS prophylaxis to a minimum of 3 cycles, and increase frequency of TLS lab monitoring. Deep vein thrombosis (DVT) prophylaxis with low dose aspirin was mandated. Steroids were allowed for management of TFR symptoms as needed. Twenty-five (25) subjects have been enrolled on the amended protocol. The median age is 60 (range 33-78), 10 subjects (40%) were Rai stage III-IV, bulky nodes were present in 9 subjects (36%), organomegaly in 23 pts (92%). Twenty-three (23) subjects have received at least 1 cycle and are evaluable for toxicity. Ten (10) subjects (43%) developed grade 3-4 neutropenia during at least 1 cycle (at doses 2.5-10 mg) which was the most common cause for dose reductions/interruptions. Six (6) subjects have required intermittent GCSF support (none requiring routine use). Three (3) subjects (13%) developed grade 3-4 thrombocytopenia (without bleeding). The most common non-hematologic toxicities were: Fatigue (74%), non-desquamating rash (48%), all were reported as grade 1-2. Infections (43%) were mostly minor non-neutropenic respiratory/sinus/skin infections. TFR occurred in 18 subjects (78%). Although most subjects experienced TFR in the first week on study, many also continued to experience flare symptoms with subsequent cycles (30.6% of all 186 cycles). Most tumor flare symptoms resolved spontaneously but eight subjects required steroids on at least one occasion with prompt resolution. Four (4) subjects were hospitalized for febrile neutropenia and/or pneumonia. No further TLS has been noted. Seventeen (17) subjects have completed at least 3 cycles and are evaluable for response. Eleven (11) subjects (65%) have achieved a PR, 6 SD (35%), and none have progressed. Responses were reached at a median of 4 cycles (range 2-15). Although dramatic lymphocyte reductions were seen as early as week 1 (lenalidomide dose 2.5 mg/d), rebound during cycle days 22-28 off-drug were common. Two subjects have withdrawn from the study due to lack of response after 10 cycles (SD) and prolonged Grade 3-4 neutropenia and thrombocytopenia, respectively. The median daily tolerated dose is 10 mg with 26% of subjects requiring dose reductions to 5 mg (most due to cytopenias).

Ferrajoli used lenalidomide as initial treatment of elderly subjects with CLL. Subjects were eligible for this study if age 65 or older and met requirements for treatment according to the 1996 NCI-WG guidelines. All subjects received lenalidomide at 5 mg daily for the first 56 days. The lenalidomide dose could then be titrated up by 5 mg increments every 28 days to reach a maximum dose of 25 mg daily. Allopurinol 300 mg daily was given from day 1-14 as TLS prophylaxis. Sixty patients were enrolled into the study. All 60 patients were evaluable for response and toxicity. Median age was 71 years (range, 66-85). The overall response (OR) rate was 60%. 5 patient (8%) achieved a complete response (CR), 5 (8%) a nodular partial response

(nPR) and 26 (43%) a PR. Median time to treatment failure was not yet reached with a median follow-up of 19 months. Grade 3-4 neutropenia, thrombocytopenia, and anemia were noted in 35%, 4%, and <1% of cycles; Grade 3-4 infections were reported in 7% of patients. There were no cases of Grade 3 or Grade 4 tumor lysis or tumor flare reactions, 30 (50%) patients experienced Grade 1 or Grade 2 tumor flare. (Badoux 2010).

5.3.2.3. Study CC-5013-CLL-001

Based on these initial data in patients with relapsed/refractory CLL, a large multicenter phase 2 study (CC-5013-CLL-001) was initiated to investigate two lenalidomide dose regimens, 10 mg daily and 25 mg x 21 days q 28 days, and confirm the efficacy and safety of lenalidomide in the treatment of relapsed/refractory CLL. The study did not include a dose escalation period. After 18 patients were enrolled into the CC-5013-CLL-001 study, four patients developed TLS of varying severity associated with concomitant TFR characterized by severe back and bone pain, with onset during the first 15 days of treatment in the first cycle of treatment. Metabolic abnormalities and/or renal dysfunction resolved with supportive therapy in 2 patients, however 2 patients died.

Similar TFR and TLS reactions have been observed with other active and immune modulating agents in CLL (Yang,1999) (Byrd, 2007) mostly occurring in early phases of treatment. The use of low dose-intensity regimens at the initiation of therapy, aggressive TLS prophylaxis, and increased patient monitoring decreased the incidence of TLS during treatment with these therapies. TFR during lenalidomide therapy has been observed in both CLL and small lymphocytic lymphoma (SLL) patients. TFR and TLS were also observed in two phase 2 studies that recently reported the effects of lenalidomide in patients with relapsed or refractory CLL (Chanan-Khan, 2006a) (Ferrajoli, 2007). In the Chanan-Khan et al. study TFR occurred in 58% of patients (Grade ≤ 2 in 50% and Grade ≥ 3 in 8%) and TLS occurred in 5% of the patients (all Grade 3). The second study by Ferrajoli et al. reported 37 % TFR (Grade ≤ 2 in 30% and Grade ≥ 3 in 7% of patients) and no TLS. Notably, the Chanan-Khan et al. study used a starting dose of 25 mg of lenalidomide given orally once daily on days 1-21 of each 28-day cycle whereas Ferrajoli et al. used a dose escalation scheme starting with 10 mg given for 21 days in the first cycle 28 day cycle followed by titration upward by 5 mg increments every 28 days to a maximum dose of 25 mg daily.

TFR in lenalidomide-treated CLL patients in clinical studies has usually been Grade 1-2 and has been well managed with non-steroidal anti-inflammatory agents or steroids.

The CC-5013-CLL-001 protocol was amended into a phase 1/2 study where the safety of several lenalidomide doses was investigated. In this study patients with prior treatment with an alkylating agent and who have failed fludarabine were started on 2.5 mg of lenalidomide daily, followed by slow intra-patient dose escalation to 5 mg after 28 days as tolerated (Wendtner, 2010). Doses were then escalated as tolerated by 5 mg every 28 days by initial cohorts of 6 patients, until the maximum tolerated dose escalation level (MTDEL) was defined or a maximum dose of 25 mg daily. Patients were treated until disease progression, and all patients received TLS prophylaxis with hydration starting 3 days prior to lenalidomide treatment and continuing for at least the first 3 cycles. The redesigned phase I study enrolled 52 patients with a median age of 65 (range, 37–80) and bulky disease (>5 cm) in 70%. Patients were heavily pretreated with a median of 4 prior therapies (range,1–14); 54% were fludarabine refractory (no-

response/relapse ≤ 6 mo), 42% had prior FCR or PCR and 21% had prior alemtuzumab. The TLS prevention strategy resulted in only 2 (3.8%) cases of TLS, both observed at 2.5 mg/daily (1 patient with Grade 2 and another with lab TLS). Grade 3/4 tumor flare occurred in 5 (9.6%) patients and was managed with NSAIDs or low-dose steroids. The most common Grade 3/4 adverse events (AEs) included neutropenia (65%) and thrombocytopenia (33%). Febrile neutropenia occurred in 4 (8%) patients. Grade 3/4 infections were observed in 21 (40%) patients; 10 (19%) patients developed pneumonia and 3 developed sepsis; 2 cases of sepsis-related death at day 37 and 94 of therapy were also noted but deemed unrelated to study drug by the investigators. Reasons for study discontinuation included disease progression (37%), AE's (29%), consent withdrawal (15%), death (4%), other reasons (10%). For 16 (31%) patients, 2.5 mg/daily was the maximum dose reached and 22 (42%) patients were unable to escalate beyond 5 mg/daily. Grade 4 neutropenia was the primary reason for delay in dose escalation. By intent-to-treat (ITT) analysis, 6 patients (12%) had a partial response (NCI-WG 1996), 30 patients (58%) had stable disease and 13 patients (25%) progressed; 3 patients were non-evaluable. Median duration of treatment was 3.1 months (range, 0.07-18.4) and the median time to response was 4.3 months (range, 2.8-7.4). Responses were observed at 10 mg/daily (n=3), at 15 mg/daily (n=1), and at 20 mg/daily (n=2); Median PFS (ITT) was 5.5 months and median PFS for responders was 12 months. Three patients still remain on therapy and were transferred to commercial lenalidomide. (Data on file at Celgene)

5.3.3. Rationale for study CC-5013-CLL-009

Patients with purine-analog or bendamustine relapsed/refractory CLL have limited therapeutic options and the addition of novel agents with alternative mechanisms of action are needed. Several studies have been conducted with lenalidomide in relapsed/refractory CLL and have demonstrated a good activity; however an optimal starting dose remains to be determined. Three different starting dose regimens of 5 mg daily, 10 mg daily and 15 mg daily respectively will be evaluated in CC-5013-CLL-009. These starting doses are based on a review by an independent external data monitoring committee (DMC) and an expert steering committee review of the safety and efficacy results of CC-5013-CLL-001 and other investigator initiated studies. These studies have demonstrated a consistent, manageable, comparable toxicity profile for subjects beginning therapy at either the 2.5 mg, 5 mg or 10 mg starting doses when adequate prophylaxis measures for TLS are implemented (increased duration of allopurinol prophylaxis with increased hydration, and increased monitoring of electrolytes with correction of electrolyte abnormalities prior to the initiation of study drug) (Ferrajoli, 2008) (Chen, 2008). Data also indicate that starting therapy at lenalidomide doses higher than 2.5 mg daily may provide superior efficacy. In light of these data, Celgene consulted expert clinicians; these experts supported a reduction in the number of dose escalation steps and thought a minimum efficacious dose to be in the range of 10 to 15 mg in relapsed CLL. As a result, CC-5013-CLL-009 was developed to study starting dose of 5 mg, 10 mg and 15 mg followed by a step-wise dose escalation to a maximum dose of 25 mg daily as tolerated to allow for fewer escalations to reach a higher dose.

This study will be conducted in accordance with "good clinical practice" (GCP) and all applicable regulatory requirements, including, where applicable, the 2008 version of the Declaration of Helsinki (see Appendix 21.2).

6. STUDY OBJECTIVES

6.1. Primary Objective

- To evaluate the safety of different lenalidomide dose regimens in subjects with relapsed or refractory B-cell CLL.

6.2. Secondary Objectives

- To evaluate the efficacy of different lenalidomide dose regimens in subjects with relapsed or refractory B-cell CLL.

7. STUDY ENDPOINTS

7.1. Primary

- Safety [type, frequency, and severity of adverse events (AEs) and relationship of AEs to lenalidomide]

7.2. Secondary

- Response rate; International Workshop on Chronic Lymphocytic Leukemia (iwCLL) Guidelines for the diagnosis and treatment of CLL (Hallek, 2008)
- Duration of response
- Time to response (TTR)
- Time to progression (TTP)
- Event-free survival (EFS)
- Progression-free survival (PFS)
- Overall survival (OS)

7.3. Exploratory

- Evaluation of response rate in predefined biologic risk group
-
- Investigate the relationship between pharmacokinetics (PK) and response (biomarkers or clinical outcomes as appropriate)
- Quality of Life

8. OVERALL STUDY DESIGN

8.1. Design Rationale

8.1.1. Study Design

CC-5013-CLL-009 is a phase 2, multicenter, randomized, double-blind, parallel-group adaptive design study that will evaluate the safety and efficacy of different lenalidomide dose regimens administered orally in subjects with relapsed or refractory B-Cell Chronic Lymphocytic Leukemia. All regimens use an intra-patient stepwise dose escalation scheme with three different initial ascending starting dose of 5 mg daily, 10 mg daily and 15 mg daily and then escalating in a stepwise manner every 28 days to reach a maximum dose of 25 mg daily based on subject tolerability. Approximately 105 subjects will be enrolled.

8.1.2. Adaptive Study Design

The CC-5013-CLL-009 phase 2 study will compare different treatment regimens (starting dose of 5 mg, 10 mg and 15 mg daily, followed by an intra-patient escalation up to a maximum of 25 mg daily) using a Bayesian approach to evaluate both efficacy and toxicity. This adaptive design will consider joint efficacy (progression rate) and toxicity outcomes to stop randomization of less promising arms (Bekele, 2008b). At any time accrual to a starting dose arm will be stopped if unacceptable toxicities are observed in that arm.

8.1.3. Randomization

Based on consideration of the Bayesian approach the following randomization schema will be followed:

- Initially subjects will be randomized (1:1:1) in a double-blind fashion to the 5 mg, 10 mg, and 15 mg starting dose arms (treatment arm 1, treatment arm 2, and treatment arm 3 respectively).
- After 18 subjects complete one 28 day cycle, an interim analysis will be conducted to review the safety of each starting dose arm(s). Subsequent interim analyses to review the safety and progression rate of each starting dose arm(s) will occur at 13-week intervals. After review of each interim analysis, a treatment arm may be dropped. At any time accrual to a starting dose arm will also be stopped if unacceptable toxicities are observed in that arm. If a treatment arm is dropped then all new subjects will be randomized equally into the remaining arm(s).

Stratification

To minimize potential imbalances within treatment groups due to select patient characteristics that may impact outcomes, study subjects will be stratified by the following criteria at randomization:

- Relapsed versus refractory to their last purine-analog or bendamustine based treatment regimen [relapsed/refractory as defined per the iwCLL guidelines for diagnosis and treatment of CLL (Hallek, 2008)]. If a subject has had prior purine-

analog based and bendamustine based regimen, the stratification will be based on subject's status post most recent regimen.

- Age < 65 years of age versus ≥ 65 years of age

8.1.4. Duration of Treatment

Subjects will receive study drug until PD or unacceptable toxicity develops. The continuation of lenalidomide treatment duration until disease progression is supported by Chanan-Khan and Ferrajoli studies which report that patients with relapsed CLL that have received lenalidomide therapy for more than one year continue to improve their response to treatment (Chanan-Khan, 2006a) (Chanan Khan, 2007) (Ferrajoli, 2008). In the Chanan-Khan study the median time to best response was 5.9 months (range 1.6 to 18.3 months). In the Ferrajoli study time to best response was 6 months in 11 patients and 9 months in 3 patients.

8.1.5. Study Population

Eligible subjects must have B-cell CLL that has relapsed after or is refractory to at least one prior CLL treatment regimen. At least one of the prior treatments must have included a purine-analog or bendamustine based treatment regimen.

8.1.6. Dose and dose interval

Depending on the starting dose, subjects will be allocated in a double-blind fashion to three different regimens and will escalate every 28 days, based on individual subject tolerability, as follows:

- Treatment Arm 1: 5 mg →10 mg →15 mg →20 mg →25 mg/daily
- Treatment Arm 2: 10 mg →15 mg →20 mg →25 mg/daily
- Treatment Arm 3: 15 mg →20 mg →25 mg/daily

Toxicities requiring dose interruption and/or modification are described in Section 10.2.3.

The rationale for the dosing for this study is discussed in Section 5.3.3 Rationale for CC-5013-CLL-009 study.

Blinding

To minimize bias for both safety and efficacy parameters based on a subject's treatment regimen, the study was a double-blinded trial. The blind was removed once all patients had completed 3 cycles of treatment.

8.1.7. Safety

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 of hematological toxicities and TLS. Hematological toxicities will be graded as specified in the iwCLL guidelines for the diagnosis and treatment of chronic lymphocytic leukemia (Hallek, 2008) (Appendix 21.4). TLS will be graded as specified by the Cairo-Bishop grading system (Appendix 21.3).

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 period. Subjects will be followed until 80% of the subjects have progressed or died or up to five years after the last subject was randomized, whichever occurs later.

8.1.8. Efficacy

Tumor response will be assessed according to the iwCLL guidelines for the diagnosis and treatment of CLL (Hallek, 2008), including CR, CRi, nPR, PR, SD, and PD. Evaluation of response will be performed after 3 cycles of therapy and every 4 weeks thereafter.

For those subjects who reach PR, CRi or CR, a CT scan of the neck, chest, abdomen and pelvis to assess lymphadenopathies will be performed at the PR and CR/CRi confirmation visits (≥8 weeks to ≤ 12 weeks after all clinical and laboratory response criteria have been met for PR or CR/CRi). Those subjects whose response was down-graded based on the CT scan interpretation at the PR or CR/CRi confirmation visit will have the CT scan repeated 4 months later at the location where remaining disease has been documented, as long as clinical and laboratory response remains present to try to document further improvement.

For those subjects who reach CR or CRi, a bone marrow aspirate and bone marrow biopsy will be performed at the CR/CRi confirmation visit (≥ 8 weeks to ≤ 12 weeks after all clinical and laboratory response criteria have been met). If the bone marrow is hypocellular, a repeat specimen should be obtained after 4 weeks, provided that the blood counts have recovered. If the bone marrow biopsy shows disease involvement (30% or greater lymphocytes, or nodules positive for B-CLL cells by immunohistochemistry), an additional bone marrow biopsy and aspirate will be taken 4 months later as long as clinical and laboratory response remain to document further improvement.

MRD status will be evaluated for those subjects who reach CR or CRi. A peripheral blood and bone marrow aspirate sample will be collected for MRD analysis by flow cytometry at the CR/CRi confirmation visit.

- If peripheral blood and bone marrow are both MRD-positive, peripheral blood samples will be repeated and assessed up to 3 additional times at 8 week intervals to try to document MRD negativity in subjects who reach confirmed CR or CRi (see Follow-up MRD assessments).
- If peripheral blood is MRD-negative and bone marrow is MRD-positive, both peripheral blood and bone marrow should be retested for MRD negativity after ≥ 12 weeks. If this repeat bone marrow is MRD-positive, no further testing for MRD will be performed.
- If both the peripheral blood and bone marrow are MRD-negative, peripheral blood will be tested every 6 months for assessment of MRD until subject discontinues study drug.

Follow-up MRD assessments:

- If any of the repeat peripheral blood assessments indicate MRD-negativity, a bone marrow aspirate sample should be collected and retested as soon as possible to confirm MRD negativity.
  - If the bone marrow is MRD-positive, both peripheral blood and bone marrow should be retested for MRD negativity after ≥ 12 weeks. If this repeat bone marrow is MRD-positive, no further testing for MRD will be performed.
  - If at any time, the bone marrow is MRD-negative, peripheral blood will be tested every 6 months for assessment of MRD until subject discontinues study drug.

Response Adjudication Committee

An independent Response Adjudication Committee (RAC) will perform a blinded, assessment of response (including assessment of SD and of PD) prior to database lock. The RAC adjudicated response data will be used in the efficacy analysis for the study.

8.1.9. Independent Data Monitoring Committee

An independent external Data Monitoring Committee (DMC) will review safety and efficacy data collected during the conduct of the study. DMC Meetings will occur approximately every 3 months during enrollment and no less than twice per year thereafter. In addition, safety data will be reviewed in an ongoing manner to assess benefit-to-risk considerations; accrual will be stopped if unacceptable toxicities are observed in a treatment arm.

8.1.10. Pharmacokinetics

Pharmacokinetic (PK) studies will be performed in up to 40 subjects. Following the enrollment of 90 subjects, participation in the PK sub-study will be mandatory for all additional subjects enrolled. Intensive sampling and sparse sampling will be discontinued as of this amendment, protocol amendment #6. Lenalidomide concentration data obtained from all visits may be used to develop the population PK model. The relationship between pharmacokinetics and response (biomarkers or clinical outcomes as appropriate) will be explored.

8.1.11. Exploratory Biomarkers

Rationale

Biomarkers are objectively measured indicators of biological or pathogenic processes, or pharmacologic responses to a therapeutic intervention. In CLL, there is particular interest in the molecular changes that may identify disease subtypes, stage of disease, or predict high-risk disease or disease progression.

Predictive Markers

Currently there are a number of biological markers useful in identifying subsets of CLL that have shortened time to treatment or increased risk of disease progression. These markers are: V_H mutational status, ZAP-70 expression, , Beta-2 Microglobulin (β2M), and genomic variations identifiable by FISH (del 13q, del 11q, del 17p, trisomy 12). These classic prognostic markers will be evaluated in this study.

8.1.12. Other Outcomes

Quality of life data will be collected as detailed in Table 2 using the FACT-Leu and EQ-5D questionnaires.

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. 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 diagnosis and treatment of CLL (Hallek, 2008)] meeting at least one of the following criteria:
   - Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia
   - Massive (i.e. > 6 cm below the left costal margin) or progressive or symptomatic splenomegaly
   - Massive nodes (i.e., > 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy
   -
   - A minimum of any one of the following disease-related symptoms must be present:
     - Unintentional weight loss ≥ 10% within the previous 6 months
     - Significant fatigue (i.e., ECOG PS 2; cannot work or unable to perform usual activities)
     - Fevers of greater than 100.5° F or 38.0° C for 2 or more weeks without other evidence of infection
     - Night sweats for more than 1 month without evidence of infection
5. Must be relapsed or refractory to at least 1 prior regimen for treatment of CLL [relapsed / refractory as defined per the iwCLL guidelines for diagnosis and treatment of CLL (Hallek, 2008)]. At least one of the prior treatments must have included a purine-analog or bendamustine based regimen
   - Relapsed is defined as a subject who has previously achieved the criteria of a complete remission (CR) or partial remission (PR), but after a period of ≥6 months, demonstrates evidence of disease progression
   - Refractory is defined as treatment failure [e.g. Stable disease (SD), nonresponse, or progressive disease] or disease progression within 6 months to the last antileukemic therapy

6. Must have an Eastern Cooperative Oncology Group (ECOG) performance status score of ≤2.
7. Females of childbearing potential (FCBP) must:
   - Have a negative medically supervised pregnancy test prior to starting study drug. She must agree to ongoing pregnancy testing during study drug therapy, and after discontinuation of study drug as specified in Appendix 21.9. This applies even if the subject practices complete and continued sexual abstinence.
   - Either commit to continued abstinence from heterosexual intercourse (which must be reviewed on a monthly basis) or agree to use, and be able to comply with, effective contraception without interruption, prior to starting study drug, during study drug therapy, and after discontinuation of study drug as specified in Appendix 21.9.
8. Male subjects must:
   - Agree to use a condom during sexual contact with a FCBP, even if they have had a vasectomy, during study drug therapy and after discontinuation of study drug as specified in Appendix 21.9.
   - Agree to not donate semen or sperm during study drug therapy and after discontinuation of study drug as specified in Appendix 21.9.
9. All subjects must:
   - Have an understanding that the study drug could have a potential teratogenic risk
   - Agree to abstain from donating blood during study drug therapy and after discontinuation of study drug as specified in Appendix 21.9.
   - Agree not to share study drug with another person
   - Be counseled about pregnancy precautions and risks of fetal exposure as specified in Appendix 21.9.

9.2. Subject Exclusion Criteria

Subjects must not meet any of the following exclusion criteria to be eligible for enrollment into the study:

1. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form
2. Active infections requiring systemic antibiotics
3. Systemic treatment for B-cell CLL within 28 days of initiation of lenalidomide treatment
4. Alemtuzumab therapy within 60 days of initiating lenalidomide treatment
5. (removed in protocol amendment #3)
6. Prior therapy with lenalidomide
7. History of grade 4 rash due to prior thalidomide treatment
8. Planned autologous or allogeneic bone marrow transplantation

9. Pregnant or lactating females
10. 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 initiating study drug
11. 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
    - Carcinoma *in situ* of the bladder
    - Incidental histologic finding of prostate cancer (TNM stage of T1a or T1b)
12. History of renal failure requiring dialysis
13. Known Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV) and/or Hepatitis C Virus (HCV) infection
14. Evidence of TLS per the Cairo-Bishop definition of laboratory TLS (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 (creatinine clearance may also be obtained by the 24-hour collection method at the investigator's discretion)
    - 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 > 1.5 x ULN
16. Uncontrolled hyperthyroidism or hypothyroidism
17. Venous thromboembolism within 12 months
18. ≥ Grade-2 neuropathy
19. Uncontrolled autoimmune hemolytic anemia or thrombocytopenia
20. Disease transformation [i.e. Richter's Syndrome (lymphomas) or prolymphocytic leukemia]

21. Participation in any clinical study or having taken any investigational therapy within 28 days prior to initiating lenalidomide therapy
22. Known presence of alcohol and/or drug abuse

10. DESCRIPTION OF TREATMENT

10.1. Description of Study Drug

Celgene Corporation will supply lenalidomide 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg and 25 mg capsules for oral administration. Subjects will receive 28 days of lenalidomide per cycle.

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

10.2. Treatment Assignments

10.2.1. Randomization

Randomization will be accomplished by a validated interactive voice response system (IVRS) to ensure timely registration and randomization. Designated site staff 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 site staff will identify the subject and confirm eligibility. When all questions have been answered, 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.

Initially subjects will be randomized (1:1:1) in a double-blind fashion to the 5 mg, 10 mg, and 15 mg starting dose arms (treatment arm 1, treatment arm 2, and treatment arm 3 respectively). Subjects will be stratified at randomization by:

- relapsed vs. refractory to their last purine-analog or bendamustine based treatment regimen (if subject has received both, the status post most recent purine-analog or bendamustine treatment regimen will be used for stratification) and
- age < 65 years of age vs. ≥ 65 years of age

After 18 subjects complete one 28 day cycle, an interim analysis will be conducted to review the safety of each starting dose arm(s). Subsequent interim analyses to review the safety and progression rate of each starting dose arm(s) will occur at 13-week intervals. After review of each interim analysis, a treatment arm may be dropped. At any time accrual to a starting dose arm will also be stopped if unacceptable toxicities are observed in that arm. If a treatment arm is dropped then all new subjects will be randomized equally into the remaining arm(s).

Site staff must contact Celgene at each visit for study drug assignment.

10.2.2. Treatment

Depending on the starting dose, each subject will be allocated in a double-blind fashion to three different regimens and will escalate every 28 days, based on individual subject tolerability, as follows:

Table 4: Dose Regimen by Treatment Arm

Dose level	Lenalidomide dose (oral administration)			Schedule
	Treatment Arm 1 5 mg starting dose arm	Treatment Arm 2 10 mg starting dose arm	Treatment Arm 3 15 mg starting dose arm	
Dose level +4	25 mg daily	25 mg daily	25 mg daily	28 days
Dose level +3	20 mg daily	25 mg daily	25 mg daily	28 days
Dose level +2	15 mg daily	20 mg daily	25 mg daily	28 days
Dose level +1	10 mg daily	15 mg daily	20 mg daily	28 days
Dose level 0	**5 mg daily**	**10 mg daily**	**15 mg daily**	**28 days**

For toxicities requiring dose interruption and/or modification (see Section 10.2.3), a more gradual stepwise dose escalation of lenalidomide (more than one 28 day cycle for each dose level) might be needed at the discretion of the treating physician due to adverse events that do not require dose reduction or interruption.

Subjects unable to escalate to the 25 mg maximum dose due to toxicity may continue with the highest dose achieved in the previous cycle or as indicated in Section 10.2.3 Dose Modification or Interruption.

10.2.3. 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 of hematological toxicities and TLS. Hematological toxicities will be graded according to iwCLL guidelines for the diagnosis and treatment of chronic lymphocytic leukemia (Hallek, 2008) (Appendix 21.4). TLS will be graded as specified by the Cairo-Bishop grading system (Appendix 21.3).

If a subject develops toxicity (see Table 5 Dose Reduction and Modification Guidelines), the dose may be reduced as outlined in Table 6 Dose Reduction Steps for Lenalidomide.

Table 5: Dose Reduction and Modification Guidelines for Lenalidomide

Toxicity	Severity	Action
Neutropenia	ANC < 500/μL	– Dose should be held (once first result of ANC showing decrease below 500/μL is present) – An additional CBC sample may be drawn at the investigator's discretion within 24 hours of the ANC decrease, prior to interruption of lenalidomide therapy, to re-monitor the ANC and confirm ANC < 500/μL – If the ANC is ≥ 500/μL (Grade 4 neutropenia not confirmed), the same dose of lenalidomide may be continued without interruption or dose reduction – If ANC is confirmed to be < 500/μL or confirmation is not required per the investigator's discretion: – Interrupt lenalidomide therapy – Follow CBC every 7 days – Resume lenalidomide (decrease one dose level) when ANC recovers to ≥ 500/μL – Use of growth factors (i.e. G-CSF) is permitted at the investigator's discretion – Re-escalation to the next consecutive dose level is permitted as follows: – If subject restarts dosing at one dose level lower on Day 1 to Day 14 of a cycle, and completes the remainder of that cycle at this lower dose without occurrence of toxicities requiring dose interruption/reduction, then the subject may be dose re-escalated by one-dose level starting at Day 1 of the subsequent cycle. – If subject restarts dosing at one dose level lower on Day 15 to Day 28 of a cycle, and completes the remainder of that cycle and the subsequent cycle at this lower dose without occurrence of toxicities requiring dose interruption/reduction, then the subject may be dose re-escalated by one-dose level starting at Day 1 of the following cycle.

Table 5: Dose Reduction and Modification Guidelines for Lenalidomide (Continued)

Toxicity	Severity	Action
Febrile Neutropenia	ANC < 1,000/μL with fever (temperature ≥ 38.5°C)	– Interrupt lenalidomide therapy – Follow CBC every 7 days – Use of growth factors (G-CSF, GM-CSF) is permitted at the investigator's discretion – Resume lenalidomide (decrease one dose level) when febrile neutropenia has resolved with ANC ≥ 500/μL – Re- escalation to the next consecutive dose level is permitted as follows: – If subject restarts dosing at one dose level lower on Day 1 to Day 14 of a cycle, and completes the remainder of that cycle at this lower dose without occurrence of toxicities requiring dose interruption/reduction, then the subject may be dose re-escalated to next consecutive-dose level starting at Day 1 of the subsequent cycle. – If subject restarts dosing at one dose level lower on Day 15 to Day 28 of a cycle, and completes the remainder of that cycle and the subsequent cycle at this lower dose without occurrence of toxicities requiring dose interruption/reduction, then the subject may be dose re-escalated to next consecutive-dose level starting at Day 1 of the following cycle.
Thrombocytopenia	Platelets < 20,000/ μL	– Interrupt lenalidomide therapy – Follow CBC every 7 days – Resume lenalidomide (decrease one dose level) when platelet count recovers to ≥ 25,000/μL – Re-escalation to the next consecutive dose level is permitted if the subject completes one full cycle without occurrence of toxicities requiring dose interruption/reduction.

Table 5: Dose Reduction and Modification Guidelines for Lenalidomide (Continued)

Toxicity	Severity	Action
Tumor Flare	Grade 3 or 4	– Interrupt lenalidomide therapy and initiate therapy with corticosteroids, NSAIDs and/or narcotics – Resume lenalidomide (decrease one dose level) when symptoms resolve to ≤ Grade 1 – Re-escalation to the next consecutive dose level is permitted at Day 1 of the subsequent cycle when Tumor Flare resolves to ≤ Grade 1.
Desquamating (blistering) rash	Any	– Permanently discontinue lenalidomide and follow for PD
Non-desquamating rash	Grade 3	– Interrupt lenalidomide therapy. – Resume lenalidomide when the rash resolves to ≤ Grade 1 (decrease one dose level)
Non-desquamating rash	Grade 4	– Permanently discontinue lenalidomide and follow for PD
Neuropathy	Grade 3	– Interrupt lenalidomide therapy. – Resume lenalidomide when the neuropathy resolves to ≤ Grade 1 (decrease one dose level)
Neuropathy	Grade 4	– Permanently discontinue lenalidomide and follow for PD
Venous thrombosis/embolism	≥ Grade 3	– Hold (interrupt) dose and start anticoagulation; – Resume lenalidomide at investigator's discretion (maintain dose level).
Hyperthyroidism or hypothyroidism	Any	– Interrupt lenalidomide and initiate appropriate medical therapy. – Resume lenalidomide at investigator's discretion (maintain dose level).

Table 5: Dose Reduction and Modification Guidelines for Lenalidomide (Continued)

Toxicity	Severity	Action

Serum Creatinine	Grade 2 (> 1.5 - 3.0 x ULN)
	
	OR
	
	Grade 3 (> 3.0 - 6.0 x ULN)
		– Interrupt lenalidomide
		– Evaluate subject weekly (minimum) until the serum creatinine return to baseline
		– If serum creatinine resolves to < Grade 1 resume lenalidomide (decrease one dose level)
		– If serum creatinine has stabilized to grade 1 after a minimum of 3 weeks of dose interruption resume lenalidomide at the investigator's discretion (decrease one dose level)
		– If serum creatinine has not stabilized to ≤ grade 1 after 5 weeks of dose interruption:
		  – Permanently discontinue lenalidomide and follow for PD at the investigator's discretion ***OR***
		  – Contact the Celgene Medical Monitor to discuss subject status
		– If the serum creatinine worsens at any time to > Grade 3, or if dialysis is indicated, permanently discontinue lenalidomide and follow for PD
		– Upon resumption of lenalidomide, evaluate subject weekly x 2 weeks to ensure the serum creatinine does not worsen; if the serum creatinine again worsens during those 2 weeks, permanently discontinue and follow for PD

Serum Creatinine	Grade 4 (> 6.0 x ULN) OR if dialysis is indicated	– Permanently discontinue lenalidomide and follow for PD

Table 5: Dose Reduction and Modification Guidelines for Lenalidomide (Continued)

Toxicity	Severity	Action
TLS	Laboratory TLS or Grade 1 TLS	– Same dose of lenalidomide will be continued without interruption or dose reduction at the investigator's discretion. – Hospitalize subjects with Grade 1 TLS, (hospitalization for laboratory TLS will be per investigator's discretion) – Provide with vigorous intravenous hydration and rasburicase therapy as needed to reduce hyperuricemia, until correction of electrolyte abnormalities. – Dose escalation to the next consecutive dose level is permitted when laboratory TLS is resolved and Grade 1 TLS is resolved to Grade 0.
TLS	≥ Grade 2	– Interrupt lenalidomide therapy. – Resume lenalidomide (at the next lower dose level) when the TLS resolves to Grade 0. – 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 re-initiation of lenalidomide. – Re-escalation to the next consecutive dose level is permitted after completion of one full cycle without laboratory TLS or ≥ Grade 1 TLS, or occurrence of toxicities requiring dose interruption/reduction.

Table 5: Dose Reduction and Modification Guidelines for Lenalidomide (Continued)

Toxicity	Severity	Action
Liver Function Tests (LFTs)	ALT > 3.0 and ≤ 5.0 x ULN **and** serum total bilirubin ≤ 1.5 x ULN	– Continue current dose level – Test at next scheduled visit
Liver Function Tests (LFTs)	ALT > 3.0 and ≤ 5.0 x ULN **and** a serum total bilirubin > 1.5 x ULN **OR** ALT > 5.0 x ULN **OR** Serum total bilirubin > 1.5 x ULN	– Interrupt lenalidomide therapy. – Evaluate ALT and serum total bilirubin weekly until both return to baseline levels – Resume lenalidomide when ALT and serum total bilirubin return to baseline. – Maintain dose level if recovery from event occurs ≤ 14 days from initial test result. – Decrease by one dose level if recovery from event is prolonged > 14 days but ≤ 28 days from initial test result. Continue to monitor weekly LFTs during this cycle. If the event does not repeat, dose escalation or re-escalation may continue according to protocol. *Medical monitor must be notified if values do not return to baseline within 28 days of the initial event.*
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)

Lenalidomide dose may be interrupted/modified per the investigator's discretion for any AE (any Grade) not outlined in Table 5.

Dose escalation or re-escalation may begin on the scheduled Day 1 of a new cycle according to the protocol guidelines if toxicities requiring dose interruption and/or modification have resolved as specified in Table 5.

If there is a dose interruption during a cycle that lasts beyond Day 28 of the cycle, the subject must still have assessments as per Table 2 every 28 days. An unscheduled visit may be conducted to meet this requirement.

If a study drug interruption has lasted for 5 weeks (35 days), the investigator should contact the medical monitor to discuss whether the subject should be continued on the study.

Table 6: Dose Reduction Steps for Lenalidomide

Dose level	Lenalidomide dose (oral administration)			Schedule
	Treatment Arm 1 5 mg starting dose arm	Treatment Arm 2 10 mg starting dose arm	Treatment Arm 3 15 mg starting dose arm	
Dose level +4 [a]	25 mg daily	25 mg daily[b]	25 mg daily[c]	28 days
Dose level +3 [a]	20 mg daily	25 mg daily	25 mg daily[c]	28 days
Dose level +2 [a]	15 mg daily	20 mg daily	25 mg daily	28 days
Dose level +1[a]	10 mg daily	15 mg daily	20 mg daily	28 days
Dose level 0	**5 mg daily**	**10 mg daily**	**15 mg daily**	**28 days**
Dose level -1	2.5 mg daily	5 mg daily	10 mg daily	28 days
Dose level -2	2.5 mg every other day	2.5 mg daily	5 mg daily	28 days
Dose level -3[d]	2.5 mg 2x per week	2.5 mg every other day	2.5 mg daily	28 days
Dose level -4[d]	Not Applicable	2.5 mg 2x per week	2.5 mg every other day	28 days

a. If a subject is at Dose Levels +1, +2, +3 or +4, a maximum of 5 consecutive dose reductions are allowed. If a 6th consecutive dose reduction is required, the subject will be discontinued from the study.
b. For the 10 mg starting dose arm, if a dose reduction is required at Dose Level +4 (25 mg daily), the subject will be dose reduced directly to Dose level +2 (20 mg daily). This will be counted as one dose reduction.
c. For the 15 mg starting dose arm, if a dose reduction is required at Dose Level +3 (25 mg daily)or Dose Level +4 (25 mg daily), the subject will be dose reduced directly to Dose level +1 (20 mg daily). This will be counted as one dose reduction.
d. If a dose reduction is required at Dose Level -4 (or at dose level -3 in the 5 mg starting dose arm) subject will be discontinued from the study.

Site staff must contact Celgene to obtain new study drug bottle for a patient. If the treatment has been withheld and the next cycle is delayed beyond 29 days after Day 1 of the prior cycle, then Day 1 of the next cycle will be defined as the first day that the treatment is resumed.

Subjects requiring dose reduction within a treatment cycle must return to the study site and return the empty bottle or any unused drug and a new bottle will be dispensed. ***Subjects will be required to return the empty bottle or any unused drug prior to new drug being dispensed.*** Subjects should take study drug from the new bottle for the remainder of the cycle (i.e. if reduction occurs on Cycle Day 16, then the subject will take study drug for days 16 though 28).

10.3. Emergency Unblinding

This is now an open label protocol. Therefore the dose of study drug will be identified on the package labeling.

10.4. Prior/Concomitant Medications

All medications (prescription and non-prescription), treatments and therapies taken from 28 days prior to Cycle 1 Day 1 through the last dose of study drug, must be recorded on the eCRF.

10.4.1. Prophylaxis and/or Treatment for TLS, TFR, Neutropenia, and Thromboembolic Events

10.4.1.1. Tumor Lysis Syndrome (TLS) Prophylaxis

TLS prophylaxis, comprising of oral hydration and allopurinol 300 mg/day will be initiated at least 3 days prior to starting study drug and for a minimum of the first 3 treatment cycles. For subjects with known allergy to allopurinol prior to study initiation or for those who develop an allergy during the course of study, the medical monitor should be contacted. 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 each cycle during the dose escalation period. 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.

Subjects will be monitored for TLS as follows:

- On Day 2 and 4 and then weekly (Days 8, 15, 22) for cycle 1 and the first cycle of each dose escalation
- On Day 1, 8 and 15 of cycle 2 (if not dose escalated)
- At least every 28 days thereafter and as clinically indicated.

10.4.1.2. Tumor Flare Reaction (TFR) Treatment

Grade 1 TFR may be treated with NSAIDs and TFR ≥ Grade 2 may be treated with corticosteroids. Narcotic analgesics may be added as needed for pain control in subjects experiencing ≥ Grade 2 TFR.

Subjects will be monitored for TFR as follows:

- On Day 2 and 4 and then weekly (Days 8, 15, 22) for cycle 1 and the first cycle of each dose escalation
- On Day 1, 8 and 15 of Cycle 2
- At least every 28 days thereafter and as clinically indicated.

10.4.1.3. Neutropenia Supportive Treatment

The use of hematopoietic growth factors is permitted. Treatment with myeloid growth factors is strongly encouraged following ASCO guidelines recommendation (Smith, 2006) for dosing and administration when the absolute neutrophil count (ANC) is less than 1,000/μL [NOTE: per the inclusion criteria, subjects must have an ANC ≥1000/μL to be eligible for study entry].

10.4.1.4. Infection Prophylaxis

Prophylactic antibiotics should be considered in subjects 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.

10.4.1.5. Thromboembolic Events Prophylaxis

Lenalidomide may increase the risk of thromboembolic events in subjects who are at high risk (high risk is defined for example as a history of a thromboembolic event and/or taking a concomitant medication associated with an increased risk for a thromboembolic event and/or a known hypercoagulable state regardless of thromboembolic history). All subjects should receive anti-thrombotic prophylaxis during study treatment. For subjects who enter the study with a platelet count close to the eligibility criteria of ≥ 50,000/ μL, the medical monitor should be contacted to discuss the anti-thrombotic prophylaxis. The recommended prophylaxis is low-dose aspirin [ASA] (70-100mg) daily; however, another prophylactic anti-thrombotic therapy may be used per investigator's discretion during study treatment. Choice of the most appropriate anti-thrombotic therapy for each subject should be based upon a careful evaluation of the different risk factors associated with each therapy, and a corresponding assessment of the individual subject's underlying medical condition. Selection should be based on the overall benefit-to-risk ratio. Use of low molecular weight heparin or warfarin (or equivalent Vitamin K antagonist) to keep the International Normalization Ratio (INR) in the range of 2-3 or other anti-thrombotic therapy according to hospital guidelines or physician preference is acceptable.

If platelets drop below 50,000/μL, the investigator should consider interrupting or adjusting the dose of anti-thrombotic therapy. In the event that platelets drop below 20,000/μL and the anti-thrombotic therapy has not already been interrupted, the investigator should again strongly consider interrupting the anti-thrombotic therapy. In addition, for platelets < 20,000/μL, lenalidomide should be interrupted and CBC should be followed every 7 days. Appropriate interventions (i.e., platelet infusion) should be considered where applicable.

10.4.1.6. Other

Other therapies considered necessary for the subject's well being may be administered at the discretion of the Investigator. These therapies may include antibiotics, analgesics, antihistamines, or other medications as well as growth factors and transfusions of red blood cells, platelets, or fresh frozen plasma given to assist in the management of complications associated with chronic lymphocytic leukemia or its therapy.

10.4.1.7. Prohibited Concomitant Therapy

Concomitant use of other CLL therapy or investigational therapies while the subject is on study drug is prohibited.

10.5. 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
- Subject withdraws consent
- Subject lost to follow-up

- Death
- Protocol violation
- Other

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

11. STUDY DRUG MATERIALS AND MANAGEMENT

11.1. Supplier(s)

Celgene Corporation will supply lenalidomide capsules.

11.2. Dosage Form

Lenalidomide will be supplied as 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg and 25 mg capsules for oral administration.

11.3. Dosage Regimen

Subjects will be randomized (1:1:1) via IVRS in a double blind fashion to receive three different starting dose of lenalidomide (5 mg daily versus 10 mg daily versus 15 mg daily) on days 1-28 of the first 28 day cycle. Subjects will then escalate every 28 days, based on individual subject tolerability, as follow (see Table 4).

- Treatment Arm 1: 5 mg →10 mg →15 mg →20 mg →25 mg/daily
- Treatment Arm 2: 10 mg →15 mg →20 mg →25 mg/daily
- Treatment Arm 3: 15 mg →20 mg →25 mg/daily

11.4. Study Drug Packaging and Labeling

The lenalidomide study drug will be packaged in bottles and each bottle will contain supplies for 28 days. 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.

Daily dispensing of capsules will be clearly defined on the bottle. Subjects requiring dose reduction within a treatment cycle must return to the study site and return the empty bottle or any unused drug and a new bottle will be dispensed. ***Subjects will be required to return the empty bottle or any unused drug prior to new drug being dispensed.*** Subjects should take study drug from the new bottle for the remainder of the cycle (i.e. if reduction occurs on Cycle Day 16, then the subject will take study drug for days 16 though 28).

11.5. Study Drug Receipt and Storage

The Investigator(s) or designee(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) or designee(s) will verify the accuracy of the information on the form and register receipt in the study drug supply system. The investigator must contact Celgene regarding any discrepancies.

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.

11.6. 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 eCRF and source documents.

11.7. 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.

11.8. Study Drug Handling and Disposal

FCBP should not handle or administer lenalidomide unless they are wearing gloves. All subjects should not extensively handle or open lenalidomide 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 the counseling of subjects. Once trained, these healthcare staff will counsel subjects prior to lenalidomide being dispensed to ensure that the subject has complied with all requirements including use of birth control and pregnancy testing (FCBP) and that the subject understands the risks associated with lenalidomide. This step will be documented with a completed lenalidomide Education and Counseling Guidance Document (Appendix 21.9), and no lenalidomide will be dispensed until this step occurs. Counseling includes verification with the subject that required pregnancy testing was performed and results were negative. A Lenalidomide Information Sheet (Appendix 21.9) will be supplied each time lenalidomide is dispensed. 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 eCRF and source documents. Celgene will provide instructions for the return of study drug supplies at the end of the study.

12. ASSESSMENT OF EFFICACY

12.1. Assessments

- Physical Exam (lymph nodes, spleen and liver measurement)
- Complete blood count (CBC) and differential
- ECOG Performance Status
- Assessment of constitutional symptoms (weight loss, fever, night sweats, fatigue)
- Computed tomography (CT) scans
- Histopathology (bone marrow aspirate/biopsy)
- Assessment for MRD by flow cytometry (peripheral blood and bone marrow aspirate)
- In addition, the following will be performed at screening:
  - Clinical staging using Rai and/or Binet as defined by the iwCLL guidelines for the diagnosis and treatment of CLL (Hallek, 2008)
  - Immunophenotyping of peripheral blood lymphocytes

12.2. Methods and Timing of Efficacy Assessments

Serial measurements of efficacy will be performed 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. Data generated by central laboratories and evaluations performed by central pathology reviewers will prevail over locally generated information in the evaluation of the subject's efficacy results. Laboratory tests that may result in dose interruption and/or modification as specified in Table 5 should also be performed locally to allow for treatment related decisions during subject visits.

At a minimum the following hematology/chemistry assessments must be performed locally: hemoglobin, absolute lymphocyte count, absolute neutrophil count and platelet count, potassium, calcium, phosphorus, creatinine, total bilirubin, AST/SGOT, ALT/SGPT, and uric acid.

At screening, subjects must meet eligibility criteria based on central lab results. At Study Day 1, subjects must meet eligibility criteria based on local or central lab results prior to initiating study therapy, however, a re-calculation of creatinine clearance is not required at Study Day 1.

Clinical response evaluations

The following assessments for evaluation of clinical response will be performed as specified in Table 2

- Physical Exam (lymph nodes, spleen and liver measurement)
- Complete blood count (CBC) and differential
- ECOG Performance Status
- Assessment of constitutional symptoms (weight loss, fever, night sweats, fatigue)

CT Scan

For those subjects who reach PR, CRi or CR, a CT scan of the neck, chest, abdomen and pelvis to assess lymphadenopathies will be performed at the PR and CR/CRi confirmation visits (≥8 weeks to ≤ 12 weeks after all clinical and laboratory response criteria have been met for PR or CR/CRi). Those subjects whose response was down-graded based on the CT scan interpretation at the PR or CR/CRi confirmation visit will have the CT scan repeated 4 months later at the location where remaining disease has been documented, as long as clinical and laboratory response remains present to try to document further improvement.. A CT scan of the neck, chest, abdomen and pelvis will be performed for all subjects, except those who discontinue due to PDs, at the treatment discontinuation visit.

The average dose of radiation exposure for a subject during CT scan of neck, chest, abdomen and pelvis is approximately 20 mSv for a 70 kg patient. However, the actual amount of radiation exposure for each subject will vary depending on, but not limited to, the size of the subject and type of CT equipment used for the assessment.

Histopathology (bone marrow aspirate/biopsy)

For those subjects who reach CR or CRi, a bone marrow aspirate and bone marrow biopsy will be performed at the CR/CRi confirmation visit (≥ 8 to ≤ 12 weeks after all clinical and laboratory response criteria have been met). If the bone marrow is hypocellular, a repeat specimen should be obtained after 4 weeks, provided that the blood counts have recovered. If the bone marrow biopsy shows disease involvement (30% or greater lymphocytes, or nodules positive for B-CLL cells by immunohistochemistry), an additional bone marrow biopsy and aspirate will be taken 4 months later as long as clinical and laboratory response remain to document further improvement.

Evaluation of MRD status

MRD status will be evaluated for those subjects who reach CR or CRi. A peripheral blood and bone marrow aspirate sample will be collected for MRD analysis by flow cytometry at the CR/CRi confirmation visit. The MRD samples will be analyzed by a local laboratory.

- If peripheral blood and bone marrow are both MRD-positive, peripheral blood samples will be repeated and assessed up to 3 additional times at 8 week intervals to try to document MRD negativity in subjects who reach confirmed CR or CRi (see Follow-up MRD assessments).
- If peripheral blood is MRD-negative and bone marrow is MRD-positive, both peripheral blood and bone marrow should be retested for MRD negativity after ≥ 12 weeks. If this repeat bone marrow is MRD-positive, no further testing for MRD will be performed.
- If both the peripheral blood and bone marrow are MRD-negative, peripheral blood will be tested every 6 months for assessment of MRD until subject discontinues study drug or the study ends.

Follow-up MRD assessments:

- If any of the repeat peripheral blood assessments indicate MRD-negativity, a bone marrow aspirate sample should be collected and retested as soon as possible to confirm MRD negativity.
  - If the bone marrow is MRD-positive, both peripheral blood and bone marrow should be retested for MRD negativity after ≥ 12 weeks. If this repeat bone marrow is MRD-positive, no further testing for MRD will be performed.
  - If at any time, the bone marrow is MRD-negative, peripheral blood will be tested every 6 months for assessment of MRD until subject discontinues study drug or the study ends.

13. ASSESSMENT OF SAFETY

13.1. Assessments

- Vital signs: pulse, blood pressure, temperature, weight and height (height at screening only)
- The following clinical laboratory assessments will be analyzed locally:
  - Hematology: hemoglobin (HGB), platelet count, absolute neutrophil count (ANC), absolute lymphocyte count (ALC)
  - Blood chemistry: potassium, calcium, phosphorus, creatinine, total bilirubin, AST/SGOT, ALT/SGPT and uric acid
  - Urinalysis: ketones, sediments and specific gravity
  - Calculated (method of Cockroft-Gault) creatinine clearance (creatinine clearance may also be obtained by the 24-hour collection method at the investigator's discretion)
  - At screening, subject must meet eligibility criteria based on central lab results. At Study Day 1, subject must meet eligibility criteria based on local or central lab results prior to initiating study therapy.
- Pregnancy testing / counseling as per Appendix 21.9
- 12-lead ECGs (performed and interpreted locally)
- Concomitant medications
- AEs by NCI CTCAE (Version 3.0) used as a guide for the grading of severity with the exceptions of hematological toxicities and TLS. Hematological toxicities will be graded as specified in the iwCLL guidelines for the diagnosis and treatment of chronic lymphocytic leukemia (Hallek, 2008) (Appendix 21.4). TLS will be graded as specified by the Cairo-Bishop grading system (Appendix 21.3).Version 3.0 with modification recommended by the iwCLL guidelines for the diagnosis and treatment of CLL (Hallek, 2008) and Cairo-Bishop grading system (for TLS).
- 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. Subjects will be followed until 80% of the subjects have progressed or died or up to five years after the last subject was randomized, whichever occurs later.

13.2. 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. Laboratory tests that may result in dose interruption and/or modification as specified in Table 5 should also be performed locally.

13.3. Recording and Reporting of Adverse Events

The recording and reporting of adverse events is described in Appendix 21.1.

14. OTHER ASSESSMENTS

14.1. Assessments Following Treatment Discontinuation

Subjects will continue in the study and receive study drug until discontinuation from the study for any of the following reasons: disease progression; AEs that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of study drug, subject withdraws consent, subject is lost to follow-up, death, protocol violation that may rule out continuation of study drug, other reasons that in the Investigators judgment that may rule out continuation of study drug.

For those subjects who discontinue study drug for reasons other than disease progression or withdrawal of consent, study visits should continue every 28 days to assess response until documentation of disease progression or until a new CLL therapeutic regimen is started, whichever comes first. During these visits only the following assessments will be required: hematology, ECOG performance status, evaluation of constitutional symptoms, physical exam for liver, spleen and lymph nodes, adverse events, second primary malignancies, concomitant medications/therapies, and assessment of response.

For subjects who develop PD characterized by transformation to a more aggressive histology [i.e. Richter's syndrome (lymphomas) or prolymphocytic leukemia], this diagnosis should be established by lymph node biopsy whenever possible.

Subjects who are discontinued from the study drug for any reason, except for withdrawal of consent, will be followed for survival, second primary malignancies and subsequent CLL therapies until the study is closed when 80% of the subjects randomized to the study have progressed or died or up to five years after the last subject was randomized, whichever occurs later.

14.2. Assessment of Pharmacokinetics

Collection of pharmacokinetic samples is discontinued as of this amendment, protocol amendment #6. Pharmacokinetic assessments will be performed in up to 40 subjects who provide consent at select centers. Following the enrollment of 90 subjects, participation in the PK sub-study will be mandatory for all additional subjects enrolled. Both intensive and sparse PK blood sampling will be performed in these subjects. All PK samples will be analyzed centrally.

Intensive PK sampling

On Cycle 1 Day 1, after an overnight fast, the subjects will receive the dose of lenalidomide in the morning at the study site and continue to fast until 3 hours post-dose. Subjects will undergo PK sampling of blood at scheduled time points for up to 8 hours post-dose (see Table 2). On Cycle 1 Day 2, all PK subjects will return to the site to provide a PK blood sample at pre-dose (equivalent to 24 hours post Day 1 dose). The following information should be recorded on Cycle 1 Day 1:

- Actual date and time of dosing

- Actual date and time for the last meal before dosing

Sparse PK sampling

Sparse PK sampling will be performed on Cycle 1 Day 4, Day 8 and Day 22, and Cycle 2 Day 8. Sparse PK sampling will be performed at Days 4, 8 and 22 of the first cycle at Dose Levels +1, +2, +3 for each Treatment Arm. If sparse PK sampling timepoints for the first cycle at Dose Levels +1, +2, +3 overlap with the Cycle 2 sparse PK sampling timepoints, only one sample is required. At each of these sparse PK sampling visits, 1 blood sample will be collected between 1 and 10 hours (inclusive) after the morning dose. For each subject, effort should be made to collect the sample in approximately 1:1 ratio between the interval 1-5 hours and the interval of 5-10 hours. On the PK visit days, subjects should take the study drug in the morning (preferably prior to their arrival at the study site). Subjects will not be required to fast for these PK visits.

Subjects will be asked to accurately provide the following information and report them to the study staff on the PK visit day for sparse PK sampling:

- Actual date and time of dosing on PK visit days and the day prior to PK visits
- Actual date and time for the last meal before dosing on PK visit days
- Actual date and time for the food eaten within 4 hours after dosing on PK visit days

Actual date and time for blood draws should be recorded. Lenalidomide concentration in plasma will be determined by a validated liquid chromatography-tendem mass spectrometry (LC-MS/MS) method.

14.3. Assessment of Exploratory Biomarkers

The following exploratory assessment will be performed as specified in Table 2.

- Blood samples for β2M will be collected at baseline.
- Blood samples for ZAP-70, V_H mutational status /TP53 mutation analysis and FISH studies for cytogenetic assessment (CCND1/IgH fusion, del 11q, del 17p, del 13q, and Trisomy 12), and confirmation of disease diagnosis by flow cytometry will be collected at baseline.

All samples will be analyzed centrally.

14.4. Assessment of Other Outcomes

Quality of Life as measured by FACT-Leu questionnaire (Appendix 21.7) and EQ-5D (Appendix 21.8) will be assessed at Cycle 1 Day 1, every 8 weeks thereafter and at treatment discontinuation.

15. STATISTICAL ANALYSES

15.1. Overview

This study will be conducted using a randomized Bayesian schedule-administration design that jointly models toxicity/response outcomes using an extension methods developed in (Bekele, 2004) (Bekele, 2005) (Bekele, 2008a) (Bekele, 2008b). Schedule-administration (or treatment strategy) designs differ from standard treatment designs in that the object of interest is not to determine if one treatment is superior to an alternative treatment, but to determine if a particular treatment administration schedule is superior to other competing schedules. In the context of the current design Celgene is interested in evaluating whether various intra-patient dose-escalation schemes are safe and effective while monitoring safety and efficacy (futility). Specifically, while treatment starts at various doses ranging from very low doses (such as 5 mg/daily) to moderately low (15 mg/daily), the goal is to perform intra-patient dose escalation (every 28 days as tolerated) until a maximum dose of 25 mg/daily is achieved. The decision to escalate is based on how well the subject tolerates the lower dose levels. While these dose escalations are taking place, toxicity and the progression rate will be monitored.

Operationally, the study will proceed as follows: Subjects will be randomized to one of the three treatment arms. The first interim analysis (toxicity only) will be performed once 18 subjects have completed one 28-day cycle. Subsequent interim analyses will occur at 13-week intervals to monitor both combined toxicity and progression rate.

- [redacted]

If a treatment arm is dropped then all new subjects will be randomized equally into the remaining arms.

[redacted]

15.2. Study Population Definitions

15.2.1. Intent-to-Treat Population

The efficacy analysis will be performed on the ITT population, which will include all subjects randomized.

15.2.2. Safety Population

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

15.2.3. Subgroup Analyses

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

- Relapsed vs. refractory to their last purine-analog or bendamustine based treatment regimen [relapsed/refractory as defined per the iwCLL guidelines for diagnosis and treatment of CLL (Hallek, 2008)]. If a subject has received both, the status post

most recent purine-analog or bendamustine treatment regimen will be used for stratification.

- Age < 65 years of age vs. ≥ 65 years of age

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

15.3. Efficacy Evaluation

Efficacy analysis will be performed on intent-to-treat population. Adjudicated response will be used for these analyses.

Response

Response, including evaluation of minimal residual disease (MRD), will be assessed by iwCLL guidelines for diagnosis and treatment of CLL (Hallek, 2008). The response rate based on the best response during the treatment period and the relative proportions in each response category will be examined. Exact test procedures for proportions will be used to compare response rate between the treatment arms. Distributions of the responses into the response categories (CR, CRi, nPR, PR, SD, PD) will be provided for each treatment arm. Response rates (CR+CRi+nPR+PR) together with confidence intervals will be provided for each regimen, both for the entire population and for the subgroups defined by the stratification factors.

Responses from subjects after they received other anti-cancer treatments will not be counted, however, these subjects will be included in the denominator.

Duration of Response

Duration of response is defined as the time from the first visit where PR, CRi, or CR was documented to PD. Duration of response will be censored at the last date that the subject was known to be progression-free for: 1) subjects who have not progressed at the time of analysis; 2) subjects who have withdrawn consent or are lost to follow-up prior to documentation of progression.

A two-sided log rank test stratified by the 3 strata used in the randomization at 0.05 significance level will be used to test the duration of response between the two treatment arms.

Time to Response

Time to response is calculated as the time from randomization to the first documented date of PR, CRi or CR based on iwCLL guidelines.

Progression-free Survival (PFS)

Progression-free survival is calculated as the time from randomization to the first documented progression or death due to any cause during or after the treatment period, whichever occurs first. The progression date will be assigned to the earliest time when any progression is observed without prior missing assessments. If withdrawal of consent or loss to follow-up occurs before documented progression or death, then these observations will be censored at the date when the last complete tumor assessments determined a lack of progression.

For subjects who do not develop progressive disease at the time of analysis, if the response from the last visit was 'not evaluable', the most prior visit date with complete evaluation indicating no progressive disease will be used as the censor date.

Event-free Survival (EFS)

Event free survival (EFS) is the interval between the start of treatment to the first sign of disease progression, or treatment for relapse, or death (whichever occurs first)

Time-to-Progression (TTP)

TTP is defined as the time from randomization to the first documented progression. For subjects who do not progress during the study, TTP will be censored at the last adequate response assessment showing evidence of no disease progression. TTP is the same as PFS when there is no death.

Overall Survival (OS)

OS 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 have withdrawn consent or 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 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 may be performed in which these subjects will be censored at the date of the first dose date of the anti-cancer therapy.

15.4. Regression Analyses

In addition we plan to perform both classical and Bayesian regression analyses in which predictors such as the stratification factors, treatment and possibly the treatment-by-stratification factor are included as covariates. Under the Bayesian framework these models will also be used to estimate posterior predictive probabilities for comparing the various treatments.

15.5. 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 patient 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.

15.6. Study Drug

Dosage statistics (mean, median, mode, standard deviation and final dose, dose at each evaluation) will be provided for each treatment arm. Time to the first dose reduction and reasons for dose reduction will be summarized for each treatment arm. Reasons for discontinuation will be summarized.

15.7. Concomitant Therapy

All concomitant treatment usage documented during the study period will be summarized in frequency tabulations for each treatment group separately. The Anatomical Therapeutical Chemical (ATC) coding scheme of the World Health Organization (WHO) will be used to group medications into relevant categories for these tabulations.

15.8. Safety Evaluation

All subjects who receive at least one dose of study drug 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.

AE frequency will be tabulated by body system, MedDRA preferred term for each treatment regimen during the Treatment Phase as well as for the Follow-up Phase when appropriate. In the by-patient 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. In the case that the AEs or event frequencies are judged to be clinically important, an exact test may be used to analyze the difference between the treatment groups.

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, and 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.

15.9. Interim Analyses

Adverse events will be summarized and assessed by the DMC first when at least 18 subjects have finished one treatment cycle. Then toxicity and progression will be assessed subsequently at 13-week intervals.

If a treatment arm is dropped then all new subjects will be randomized equally into the remaining arms.

The interim analyses will be performed by a third party statistician not affiliated with Celgene.

15.10. Sample Size and Power Considerations

The sample size will be approximately 105 subjects, 35 per arm, barring early stopping. The original accrual rate was assumed to increase with time such that approximately 9-12 subjects will accrue in the first 3 months and a total of 41 to 55 subjects will accrue by 6 months with the remainder accruing by 60 weeks. Therefore, in addition to monitoring toxicity and progression, the accrual rate will be monitored.

15.11. Other Topics

15.11.1. Pharmacokinetics Analysis:

If the data are sufficient, noncompartmental PK parameters, such as T_{max}, C_{max}, AUC, CL/F, and $t_{1/2}$, will be estimated. Descriptive statistics will be provided for plasma concentrations and PK parameters. Lenalidomide concentration data obtained from all visits may be used to develop the population PK model. The relationship between pharmacokinetics and response (biomarkers or clinical outcomes as appropriate) will be explored. Detailed methodology will be outlined in a separate PK data analysis plan and the results will be presented in a stand-alone PK report.

15.11.2. Exploratory Analysis

16. QUALITY CONTROL AND QUALITY ASSURANCE

16.1. 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, eCRFs, 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, eCRFs, 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.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the eCRF 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 eCRFs or via source data clarification forms 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.

16.2. 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 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, eCRFs and applicable supporting records of subject participation for audits and inspections by IRB/IECs, regulatory authorities (e.g. FDA, EMA) 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.

16.3. Investigator(s) Responsibilities

Investigator responsibilities are set out in the 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 on the Screening Log provided by Celgene.

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 eCRFs supplied by Celgene. The data on the eCRF 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 (e.g., medical records, office charts, hospital charts, and study related charts) for source data verification. The eCRFs 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.

17. REGULATORY CONSIDERATIONS

17.1. 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 (see Appendix 21.2). 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 Subjects and Part 56 Institutional Review Boards. Before implementing this study, the protocol, the proposed informed consent form(s) 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.

17.2. Protocol Amendments

Any amendment to this protocol that seems appropriate, as the study progresses (e.g. 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. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

17.3. 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 21 CFR Parts 50 and 56 and ICH guidelines.

Documentation that informed consent occurred prior to any study specified screening procedures 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.

17.4. Subject Confidentiality

Celgene affirms the subject'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 subject's statement of informed consent, it is the responsibility of the Investigator(s) to obtain such permission in writing from the appropriate individual.

18. DATA HANDLING AND RECORDKEEPING

18.1. 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, that is, copies of eCRFs and source documents, original documents, data, and records (e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject'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; subject files) and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study are complete, accurate, and filed and retained.

18.2. Data Management

Data will be entered into the clinical database per the guidelines established for the study. 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 staff. 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 appropriate SOP(s) for the study.

18.3. 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, monitor 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 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 (i.e., 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.

19. PREMATURE DISCONTINUATION OF THE STUDY

19.1. 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

19.2. 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 (e.g., IRB/EC, regulatory authorities, etc.).

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21. APPENDICES

21.1. 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 the signing of informed consent 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 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 signing of informed consent to the treatment discontinuation visit. All AEs that lead to study discontinuation should be followed until resolution or stabilization. For subjects who discontinue study treatment but continue to be followed every 28 days until PD or new CLL therapy, AEs will be reported until 30 days post last dose of study drug or until study discontinuation, whichever occurs last. SAEs will be reported from time informed consent form is signed to 30 days post last dose of study drug. SAEs will be reported at any time post last dose of study drug if it is considered related to study drug. AEs will be recorded on the AE page of the eCRF 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 eCRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE.

Serious adverse event

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

- Results in death
- Is life-threatening (i.e., 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 80% of the subjects have progressed or died or up to five years after the last subject was randomized, whichever occurs later. 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 (e.g., 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 eCRF 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 of hematological toxicities and TLS. Hematological toxicities will be graded as specified in the iwCLL guidelines for the diagnosis and treatment of chronic lymphocytic leukemia (Hallek, 2008) (Appendix 21.4). TLS will be graded as specified by the Cairo-Bishop grading system (Appendix 21.3). 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

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 an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE pages of the eCRF. 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 last dose of study drug, 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 80% of the subjects have progressed or died or up to five years after the last subject was randomized, whichever occurs later. 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 (e.g., any confirmatory histology or cytology results).

The SAE must be reported immediately (i.e., within 24 hours of the Investigators' knowledge of the event) to the Celgene Safety Monitor by telephone and facsimile. A phone call is to be made to the Safety Monitor and 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 30 days of the subject's last dose of study drug, 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 phone and 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 the Celgene Safety Monitor 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 an SAE (i.e., 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 (i.e., report the event to the Celgene Safety Monitor by telephone and 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 the Celgene Safety Monitor by telephone and 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 events suspected of being related to lenalidomide based on the Investigator Brochure.

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 studies 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, i.e., 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.

Celgene safety contact information

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

21.2. Declaration of Helsinki

The Declaration of Helsinki can be found at: http://www.wma.net/e/policy/b3.htm

21.3. Cairo-Bishop Definition and Grading of Tumor Lysis Syndrome (Cairo, 2004)

Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome (LTLS)

Uric Acid	≥ 476 µmol/l (≥ 8.0 mg/dl) or 25% increase from baseline
Potassium	≥ 6.0 mmol/l (≥ 6.0 mEq/l) or 25% increase from baseline
Phosphorous	≥1.45 mmol/l (≥ 4.5 mg/dl) or 25 % increase from baseline
Calcium	≤ 1.75 mmol/l (≤ 7.0 mg/dl) or 25% decrease from baseline
Laboratory tumor lysis syndrome (LTLS) is defined as either a 25% change or level above or below normal, as defined above, for any two or more serum values of uric acid, potassium, phosphate, and calcium within 3 days before or 7 days after the initiation of chemotherapy. This assessment assumes that a patient has or will receive adequate hydration (± alkalinization) and a hypouricaemic agent(s).	

Cairo-Bishop Definition of Clinical TLS

The presence of laboratory TLS and one or more of the following criteria:
1. Creatinine: ≥ 1.5 ULN (age > 12 years or age adjusted) 2. Cardiac arrhythmia / sudden death 3. Seizure*

ULN, Upper limit of normal

*Not directly attributable to a therapeutic agent

Cairo-Bishop Grading System for TLS

Grade	LTLS	Creatinine	Cardiac Arrythmia	Seizure
0	-	≤ 1.5 x ULN	None	None
1	+	1.5 x ULN	Intervention not indicated	None
2	+	> 1.5 – 3.0 x ULN	Non-urgent medical intervention indicated	One brief generalized seizure; seizure(s) well controlled or infrequent; focal motor seizures not interfering with ADL
3	+	> 3.0 – 6.0 x ULN	Symptomatic and incompletely controlled medically or controlled with device	Seizure in which consciousness is altered; poorly controlled seizure disorder; breakthrough generalized seizures despite medical intervention
4	+	> 6.0 x ULN	Life-Threatening	Seizures of any kind that are prolonged, repetitive, or difficult to control
5	+	Death*	Death*	Death*

LTLS, laboratory tumor lysis syndrome; ULN, upper limit of normal; ADL, activities of daily living

*Probably or definitely attributable to clinical TLS

21.4. Grading of Hematological Toxicity (Hallek, 2008)

Grade[a]	Decrease in Platelets[b] or Hb[c] (nadir) From Pretreatment value (%)	Absolute neutrophil count/µL[d] (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

a. 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.

b. 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 (e.g., 20,000/µL) was present pretreatment, in which case the patient is not evaluable for toxicity referable to platelet counts.

c. 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.

d. 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.

21.5. 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, e.g., 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

21.6. Clinical Staging of CLL Patients

21.6.1. Rai staging system (modified) (Rai, 1987)

Low-risk disease	Lymphocytosis with leukemia cells in the blood and/or marrow (lymphoid cells > 30%)
Intermediate risk disease	Lymphocytosis, enlarged nodes in any site, and splenomegaly and/or hepatomegaly (lymph nodes being palpable or not)
High risk disease	Disease-related anemia (as defined by hemoglobin level less than 11 g/dl or thrombocytopenia (as defined by platelet count of less than 100 x 10^9 / L)

21.6.2. Binet staging system (Binet, 1981)

Staging is based on the number of involved areas, as defined by the presence of enlarged lymph nodes of > 1 cm in diameter or organomegaly, and on whether there is anemia or thrombocytopenia.

Area of involvement considered for staging:

1. Head and neck, including the Waldeyer ring (this counts as one area, even if more than one group of nodes is enlarged)
2. Axillae (involvement of both axillae counts as one area)
3. Groins, including superficial femorals (involvement of both groins counts as one area)
4. Palpable spleen
5. Palpable liver (clinically enlarged)

Stage A	Hemoglobin ≥ 10 g/dL and platelets ≥ 100 x 10^9/L and up to two of the above areas involved
Stage B	Hemoglobin ≥ 10 g/dL and platelets ≥ 100 x 10^9/L and organomegaly greater than that defined for stage A (i.e. three or more areas of nodal or organ enlargement)
Stage C	Hemoglobin < 10 g/dL and/or platelet count < 100 x 10^9/L, irrespective of organomegaly

21.7. FACT-Leu Questionnaire

FACT-Leu (Version 4)

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

English 2/8/2005

FACT-Leu (Version 4)

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-Leu (Version 4)

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
BRM 3	I am bothered by fevers	0	1	2	3	4
P2	I have certain parts of my body where I experience significant pain	0	1	2	3	4
BRM 2	I am bothered by the chills	0	1	2	3	4
ES3	I have night sweats	0	1	2	3	4
LEU 1	I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin)	0	1	2	3	4
TH1	I bleed easily	0	1	2	3	4
TH2	I bruise easily	0	1	2	3	4
HI 12	I feel weak all over	0	1	2	3	4
BMT 6	I get tired easily	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
N3	I worry about getting infections	0	1	2	3	4
LEU 5	I feel uncertain about my future health	0	1	2	3	4
LEU 6	I worry that I might get new symptoms of my illness	0	1	2	3	4
BRM 9	I have emotional ups and downs	0	1	2	3	4
LEU 7	I feel isolated from others because of my illness or treatment	0	1	2	3	4

English
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2/8/2005
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21.8. EQ-5D Health Questionnaire

Health Questionnaire

(English version for the UK)

(validated for use in Eire)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

21.9. Pregnancy Prevention Risk Minimization Plans

21.9.1. Lenalidomide Pregnancy Prevention Risk Management Plan

21.9.1.1. Lenalidomide Pregnancy Risk Minimisation Plan for Celgene Clinical Trials

Section 21.9.1 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 21.9.1.2);
2. Lenalidomide Education and Counseling Guidance Document (Section 21.9.1.3);
3. Lenalidomide Information Sheet (Section 21.9.1.4).

1. The Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods document (Section 21.9.1.2) 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 21.9.1.3) 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 21.9.1.4) 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.

21.9.1.2. 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 (i.e., 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 (i.e., 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 21.9.1.2).
- 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 (i.e., 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 (i.e., 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 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 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 10-14 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.

21.9.1.3. 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 (i.e., 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 risk 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 risk 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 lenalidomide 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.

21.9.1.4. 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 contract 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 lenalidomide**
- 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.

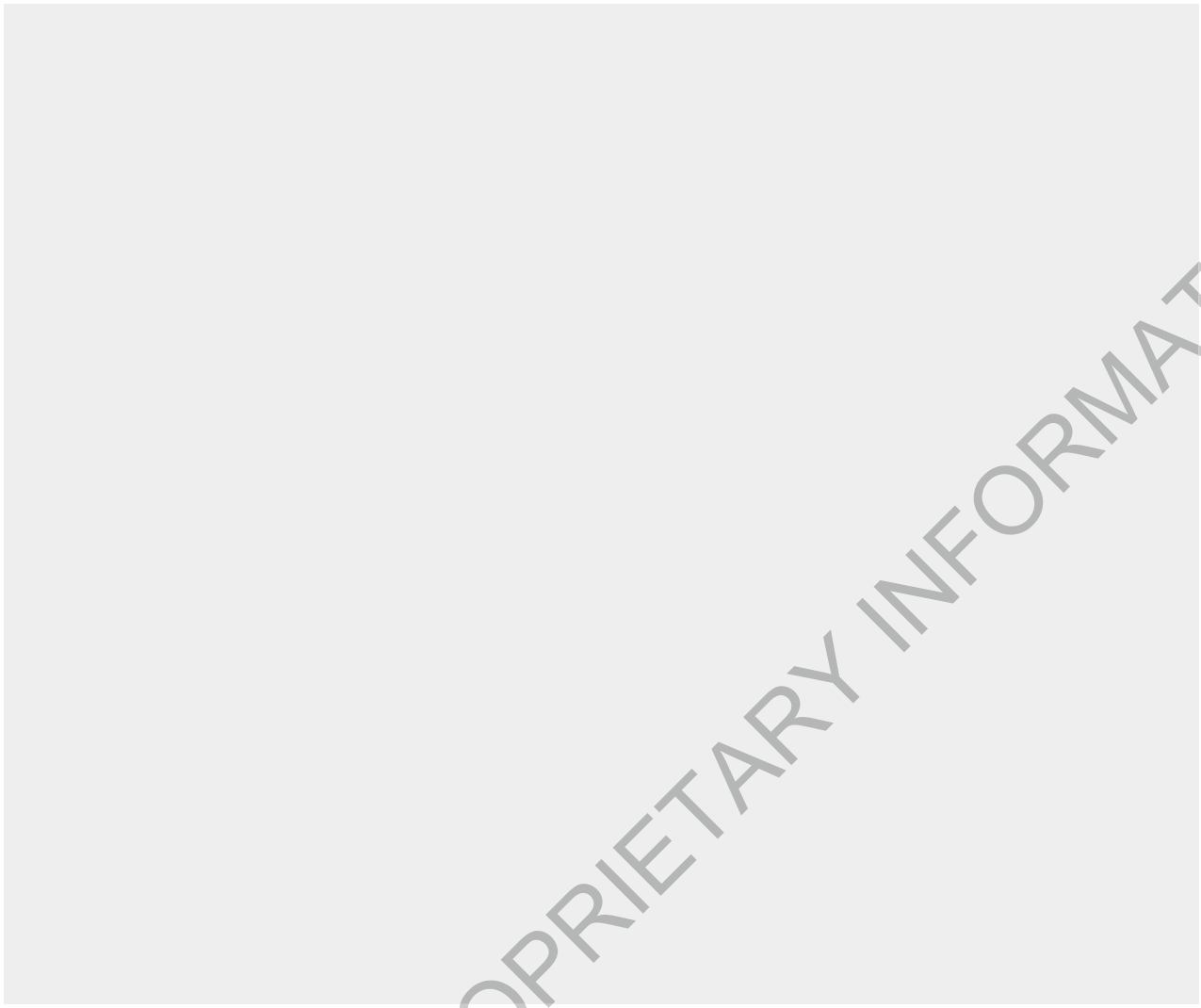
If you are a male:

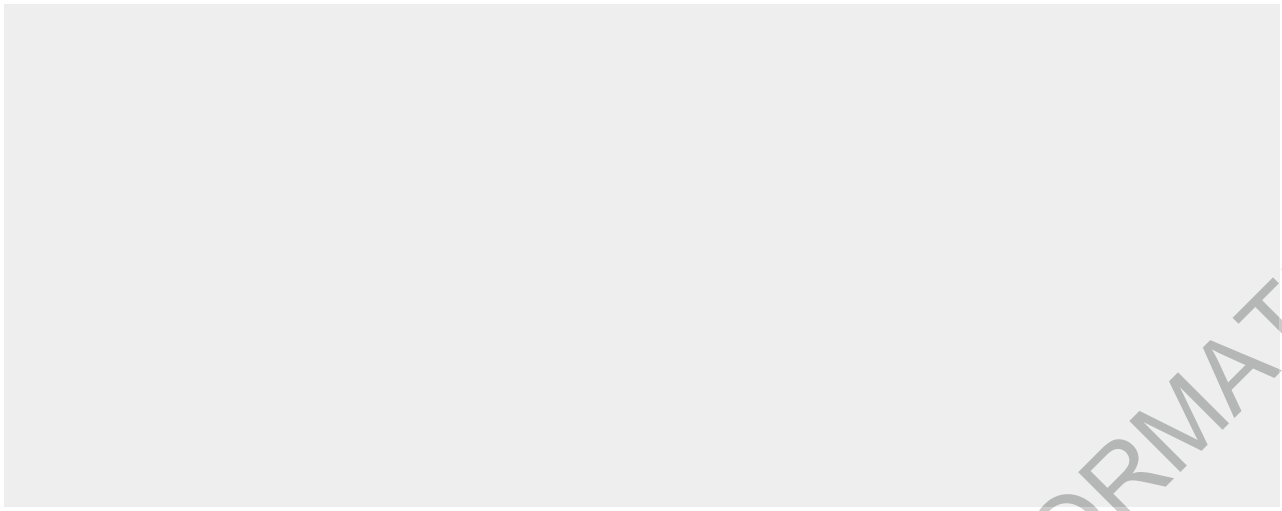
Lenalidomide is detected in trace quantities in human semen. The risk to the foetus in females of child bearing potential whose male partner is receiving lenalidomide is unknown at this time.

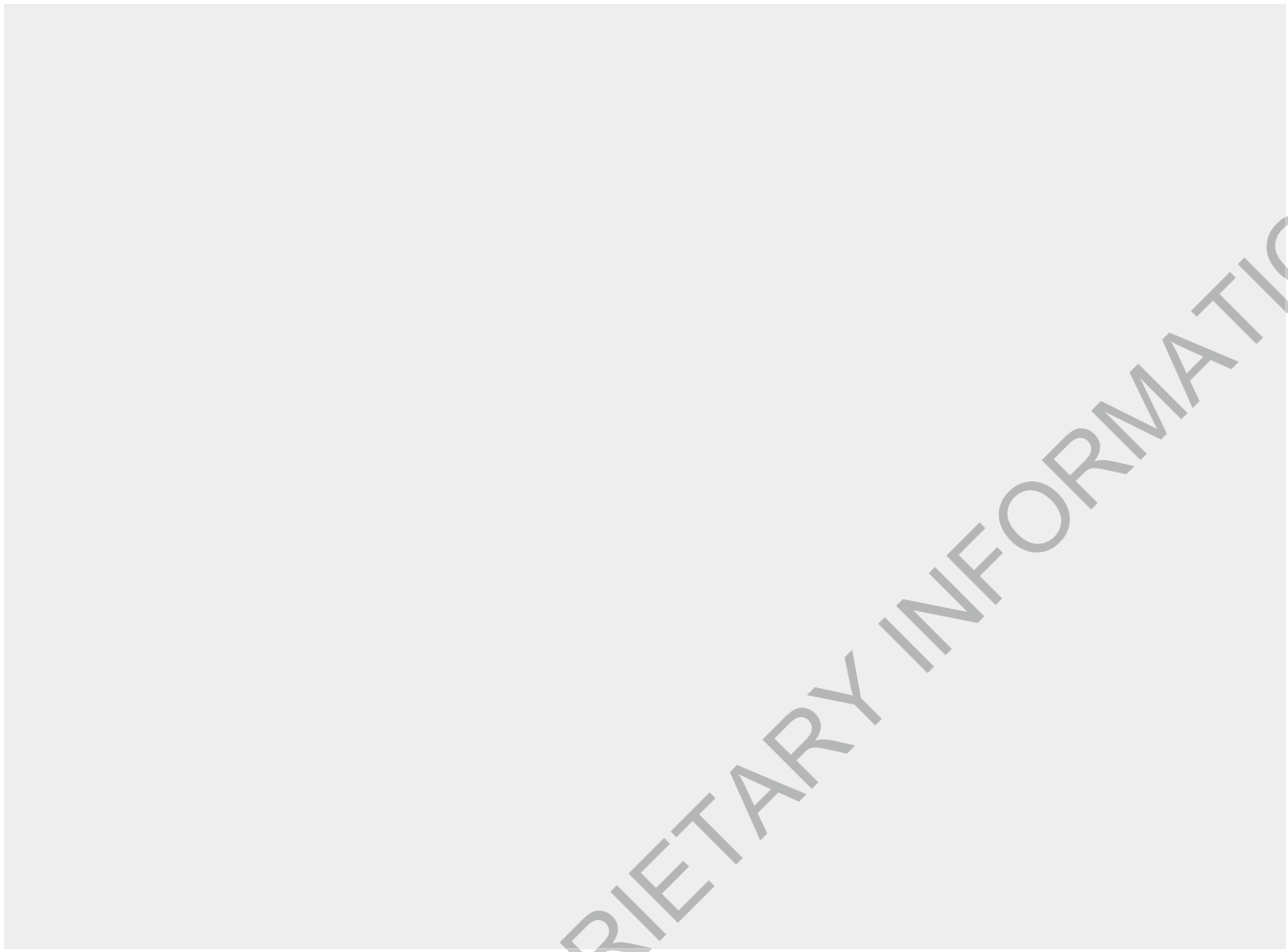
- Male patients (including those who have had a vasectomy) must practice complete abstinence or must use a condom during sexual contact with a pregnant female or a female who that can become pregnant:
  - While you are taking study drug
  - During dose interruptions of study drug
  - For 28 days after 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**

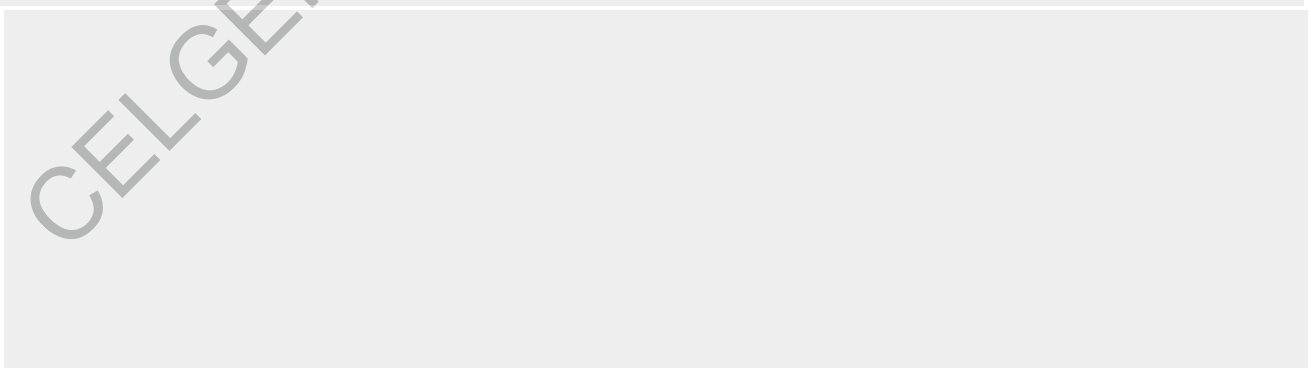
2. **Restrictions in sharing study drug and donating blood:**
   - **Do not share study drug with other people. It must be kept out of the reach of children and should never be given to any other person.**
   - **Do not donate blood** while you take study drug and for 28 days after stopping study drug.
   - **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.

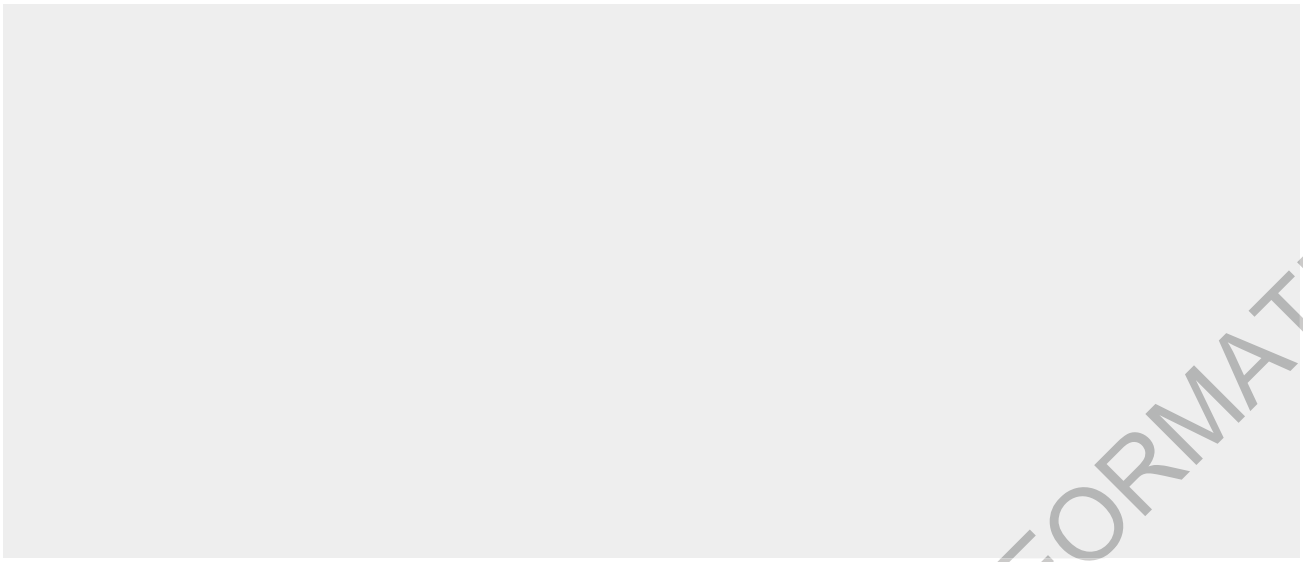
   Additional information is provided in the informed consent form and you can ask your study doctor for more information.











Celgene Signing Page

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

UserName:
Title:
Date: Tuesday, 19 May 2015, 11:41 AM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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1. JUSTIFICATION FOR AMENDMENT

The CC-5013-CLL-009 protocol has been ongoing since 2009. The intent of the protocol amendment is to facilitate the ongoing conduct for the patients that remain on study drug.

The key change in this protocol amendment is to change the study drug packaging from blister cards with matching placebo capsules to bottles. This will reduce the number of capsules patients are required to take each day.

The amendment further clarifies that patients currently on study drug may remain on study drug, beyond the 80% event milestone, until final completion of the study at which time they may transition to non-study lenalidomide. The transition will be at the discretion of the site primary investigator and any local regulations.

Significant changes included in this protocol amendment #6 are summarized below:

- IVRS will be discontinued for this protocol. Sites will order study drug when needed through Celgene investigational drug dispensing program. This will permit sites to order study drug only when needed rather than maintain a stock of study drug for the IVRS to allocate. The change is possible at this time since few patients remain on study drug and the study drug is no longer blinded.
- Removed the 1.25-mg dose level and applied corresponding changes in the Dose Reduction Steps for Lenalidomide (Table 6) as no patients utilize this dose level.
- As all subjects are beyond the risk for TLS, Celgene will no longer provide allopurinol supply for site outside of North America.
- Remove lymph node biopsy and fine needle aspirate assessments as no patients consented for these additional tests.
- Remove additional PK sample collection. PK samples were drawn at study day 1 and at dose escalation. Since the last patient randomized was 2012, further dose escalations are not anticipated and hence no further PK samples. This will permit the final analysis and reporting of this exploratory endpoint at this time.
- Remove the requirement to submit blood samples (hematology, chemistry, thyroid hormone, MRD), urine (urinalysis) and bone marrow (biopsy and aspirate) samples to central lab for analysis. Local labs will continue to be collected in this protocol. The purpose of this change is to simplify the protocol procedures in effort to reduce the workload for the site personnel.
- Tumor flare events are anticipated at the start of study drug administration. Since the last patient randomized was 2012, additional events of tumor flare are not anticipated. The purpose of this change is to simplify the protocol procedures in effort to reduce the workload for the site personnel.
- Remove the text for blinding and emergency unblinding activities as the protocol is unblinded.

- Change of Medical Monitor
- Changes for grammar and topographical errors

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- **Increased the sample size and required that following the enrollment of 90 subjects, participation in the PK sub-study will be mandatory.**

At least 6 subjects per treatment arm are needed to provide evaluable PK data. At the time of this amendment, a sufficient number of patients have not been enrolled into the PK sub-study. The protocol sample size will be increased to collect additional PK subject samples. Enrollment will be extended to only those subjects who agree to participate in the PK sub-study.

- ***Clarify that the second primary malignancy assessment should be completed during the progression free survival follow up phase and the survival phase***

Clarified that the assessment for second primary malignancy should be completed during the 28-day follow up visits for all patients that discontinue the treatment phase for reasons other than progression of disease or withdraw of consent.

Additionally, the assessment for second primary malignancy should be completed for all subjects in the survival phase regardless of the reason for study discontinuation. These assessments were already included in Amendment 4 (but not specified in each sentence that mentioned the respective follow up).

- ***Clarify the schedule for the baseline bone marrow biopsy and aspirate***

The bone marrow biopsy and aspirate may be completed either during the screening phase or may be completed once the patient has been confirmed as eligible and entered into the study. The bone marrow biopsy and aspirate procedures are an invasive procedure. The results are not specifically part of the inclusion exclusion criteria. This change is being implemented to avoid unnecessary sampling for a subject who may eventually fail screening and not enter the study.

- ***Expanded exclusion criteria surrounding history of prior malignancies from 2 years to 5 years.***

Recent multivariate analyses conducted by Celgene have demonstrated that patients with a history of prior invasive malignancies are at risk for developing another malignancy during lenalidomide-containing therapy. As a result, various Health Authorities have requested that Celgene amend protocols to exclude patients who have a history of malignancies within the 5 years prior to starting the trial.

- ***Update study contact information***

Contact information was updated to reflect the new Clinical Research Physician and Study Manager.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- ***Require that second primary malignancies be treated as SAEs and reported throughout the study duration..***

There have been reports of second primary malignancies in clinical studies with lenalidomide. As it is unclear whether lenalidomide increases the risk of second primary malignancies, Celgene is asking that all subjects in all study treatment arms be followed to confirm if a diagnosis of a second primary malignancy has occurred. The protocol duration was amended to provide up to 5 year follow up for each subject.

In order to monitor and thoroughly evaluate all second primary malignancies that occur in subjects receiving any study medication, the protocol is being amended to require that second primary malignancies are assessed at every study visit and reported as serious adverse events at any time during the study, including from the time of signing the Informed Consent Form up to and including the survival follow up phase.

- ***Incorporate the current Celgene Pregnancy Prevention Plan language regarding the risks of lenalidomide***

In order to ensure consistency in the pregnancy prevention guidelines across all countries, the Pregnancy Prevention Plan was updated to a global template where information provided to risk counselors is identical regardless of country. The European guidelines from the previous version of the protocol have been eliminated and the previously labeled, 'ex-European' guidelines have now been adopted in all countries. Several other minor changes have been made, including replacing the term 'lenalidomide' with study drug, where appropriate, replacing the term Investigator with 'study doctor', where appropriate and eliminating the Lenalidomide Patient Card.

- ***Incorporated the current Celgene language regarding source data verification.***

The source data verification plan was updated to provide greater flexibility in remote monitoring of the study data.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- Based on delayed enrollment, an administrative decision was made to decrease the number of planned subjects from up to 120 to up to 90.
- The frequency of visits during Cycles 2, 3 and 4 were decreased. The frequent visits during initial cycles were implemented to monitor for Tumor Lysis Syndrome (TLS) and Tumor Flare Reaction (TFR) based on data from the original design of the CC-5013-CLL-001 (CLL 001) study:
  - In the original protocol design for CLL-001, patients were randomized to 10 mg lenalidomide/daily or 25 mg lenalidomide days 1-21 out of 28 days study (n=18). Five (5) cases of TLS were observed. Four (4) out of the total 5 cases of TLS occurred during the first 15 days of initiating lenalidomide, and 1 occurred on day 45. There was only one reported case of serious TFR occurring on day 4. In the amended CLL 001 study design (n=52), patients starting at 2.5 mg lenalidomide /daily with incremental escalation up to a maximum of 25 mg lenalidomide/daily as tolerated. Data from the amended protocol include, one case of lab TLS at day 7 and one case of clinical TLS (Grade 2) at day 8. Of the 7 total cases of serious TFR, 6 occurred during the first 15 days of initiating lenalidomide and one occurred > 15 days after initiating lenalidomide.
  - Data from the amended CLL-001 protocol indicate some of the frequent visits can be eliminated to decrease the burden of frequent visits on subjects. The Cycle 2 Day 22 visit and the weekly (Day 8, 15, 22) visits during Cycle 3 and Cycle 4 will no longer be required. The Day 2, 4, 8, 15, 22 visits during Cycle 1 and at the first cycle of each dose escalation and Day 8 and 15 visits during Cycle 2 will remain to cover the timeframe at which TLS and serious TFR were reported in the CLL 001 study.
- Changes to the eligibility criteria:
  - The cap on the number of prior treatment regimen for B-CLL was removed. Investigators participating in the CLL 009 study have commented that patients often have >4 prior treatments at the time they are considered for protocol therapy for relapsed/refractory CLL. This is based on the availability and use of fludarabine, alemtuzumab, rituximab, bendamustine and ofatumumab as monotherapy or in combination. Allowing more than 4 prior treatment regimens for B-CLL will provide more heavily pre-treated patients the option to be screened and enrolled into the study.
  - Previously, the inclusion criteria required that subjects had prior treatment with a purine-analog based regimen. The protocol was updated to allow inclusion of subjects with prior treatment with either a purine-analog or bendamustine based treatment regimen. The FDA approved bendamustine in 2008 for the first-line treatment of patients with CLL and in March 2010 the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA)

issued a positive opinion on a referral procedure recommending that marketing authorizations should be granted for bendamustine in CLL. The marketing authorizations will be issued on a national basis through decentralized procedure.

- Based on above noted change, the stratification factor will be updated to include relapsed vs. refractory to a purine-analag or bendamustine based treatment regimen (if subject has received both, status post most recent purine-analog or bendamustine treatment regimen will be used).
- The 120 days washout for prior alemtuzumab treatment will be decreased to 60 days. The protocol already requires 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 during study. The decrease in wash-out period will allow subjects who need more immediate treatment post alemtuzumab to be screened and enrolled into the study.
- The inclusion criteria was changed to allow screening of subjects with prior history of in carcinoma *in situ* of the bladder if the subject has been disease free for < 2 years prior to enrollment into the study. This exception was already present for carcinoma *in situ* of the cervix and breast, and was extended to include the bladder to avoid unnecessary exclusion of subjects for a prior malignancy that will not impact the safety or efficacy evaluations within the study.

- Since this is a Phase 2 study, an administrative decision was made for the following:
  - Study will be closed once 80% of the subjects randomized to the study have progressed or died. All subjects ongoing on study drug at the time the study is closed will be transferred to commercial drug on a free basis. The survival follow-up will also cease at the time of study closure.
  - CT Scans for lymph nodes, liver and spleen will not be reviewed centrally.
-
- The sampling for prognostic factors (Beta-2 microglobulin, ZAP-70, V_H Mutation status/TP53, FISH analysis for cytogenetics) and confirmation of disease diagnosis will be performed at baseline (Study Day 1 pre-dose) instead of during screening. This change is being implemented to avoid unnecessary sampling for subject who may eventually fail screening and not enter the study.

-
- The sampling time points for and sparse pharmacokinetics were updated due to change in visit schedule for Cycles 2, 3 and 4.
- Minor editorial clarifications are also included in this amendment.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- For select exploratory assessments the following changes were implemented:
  -
  - Tumor Protein (TP) 53 mutation analysis was added to the protocol based on recent publications and presentation at major international hematology meetings in 2009 showing the importance of studying TP53 mutational status in addition to the 17p deletion as an important prognostic factor in the B-CLL patient population[1]. The TP53 mutation analysis will be performed at screening on the same sample as those collected for the VH mutational status analysis and will not require additional blood sampling.
  - Added to the protocol V_H mutational status /TP53 mutation analysis and FISH studies.
  -
- The maximum number of prior treatment regimen for B-CLL was increased from 3 to 4. This will allow more heavily pre-treated patients to be considered and enrolled into the study.
- In light of the protocol requirement to implement anti-thrombotic prophylaxis for all subjects enrolled, additional guidance was added to emphasize the importance of monitoring patients' platelet counts during the study.
- The 24 hour emergency call center information has been added to the protocol as this is now implemented for all Celgene-sponsored studies to ensure patient safety.
- Added further details on when study drug should be permanently discontinued in case of renal insufficiency.
- Added details on AE reporting timeframes required for the study.

The amendment also includes several other minor clarifications and corrections

[1]Zenz T, Mohr J, Edelmann J, et al. Treatment resistance in chronic lymphocytic leukemia-the role of the p53 pathway. *Leukemia and Lymphoma.* 2009 March, 50(3): 510-513.

SUMMARY OF CHANGES
PROTOCOL CC-5013-CLL-009 AMENDMENT 1

A PHASE 2, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP STUDY OF THE SAFETY AND EFFICACY OF DIFFERENT LENALIDOMIDE (REVLIMID®) DOSE REGIMENS IN SUBJECTS WITH RELAPSED OR REFRACTORY B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA

Amendment # 1: 10 June 2009

Section	Previous Text	Revised Text	Rationale for change
Table 1: Celgene Emergency Contact Information 24-Hour emergency contact	Celgene Corporation 86 Morris Avenue Summit, New Jersey 07901	North America Primary Contact Celgene Corporation 86 Morris Avenue Summit, New Jersey 07901 North America Back-up Contact Europe 24-Hour Contact	Added back-up North American and 24 hour European emergency medical contacts.

Section	Previous Text	Revised Text	Rationale for change
Synopsis Table 2 Schedule of Assessments (footnote c) 14.1 Assessments Following Treatment Discontinuation	For those subjects who discontinue study drug for reasons other than disease progression or withdrawal of consent, study visits may continue every 28 days to assess response until documentation of disease progression or until a new CLL therapeutic regimen is started, whichever comes first. During these visits for these subjects some safety evaluations are no longer required to be performed (including thyroid function tests, chemistry, urinalysis, pregnancy testing/counseling, adverse event collection, concomitant medication collection); however; SAEs related to study procedures will continue to be recorded up to the time of PD or until a new treatment is instituted, whichever come first.	For those subjects who discontinue study drug for reasons other than disease progression or withdrawal of consent, study visits may continue every 28 days to assess response until documentation of disease progression or until a new CLL therapeutic regimen is started, whichever comes first. During these visits only the following assessments will be required: hematology, ECOG performance status, evaluation of constitutional symptoms, physical exam for liver, spleen and lymph nodes, adverse events, concomitant medications/therapies, and assessment of response.	Updated to clarify which assessments may be performed for subject who discontinue from the study but continue to be assessed for response until disease progression.
Synopsis 10.5.1.5. Thromboembolic Events Prophylaxis	**Thromboembolic Events Prophylaxis** Lenalidomide may increases the risk of thromboembolic events in subjects	**Thromboembolic Events Prophylaxis** Lenalidomide may increase the risk of thromboembolic events in subjects	Update to allow greater investigator discretion in determining thromboembolic

Section	Previous Text	Revised Text	Rationale for change
	who are at high risk (high risk is defined for example as a history of a thromboembolic event and/or taking a concomitant medication associated with an increased risk for a thromboembolic event and/or a known hypercoagulable state regardless of thromboembolic history). All subjects will be required to receive prophylactic aspirin [ASA] (70-100mg) daily unless contraindicated. If ASA is contraindicated, use of low molecular weight heparin or warfarin (or equivalent Vitamin K antagonist) to keep the International Normalization Ratio (INR) in the range of 2-3 or other anti-thrombotic therapy according to hospital guidelines or physician preference is acceptable.	who are at high risk (high risk is defined for example as a history of a thromboembolic event and/or taking a concomitant medication associated with an increased risk for a thromboembolic event and/or a known hypercoagulable state regardless of thromboembolic history). All subjects should receive anti-thrombotic prophylaxis during study treatment. The recommended prophylaxis is low-dose aspirin [ASA] (70-100mg) daily; however, another prophylactic anti-thrombotic therapy may be used per investigator's discretion during study treatment. Choice of the most appropriate anti-thrombotic therapy for each subject should be based upon a careful evaluation of the different risk factors associated with each therapy, and a corresponding assessment of the individual subject's underlying medical condition. Selection should be based on the overall benefit-to-risk ratio. Use of low molecular weight heparin or warfarin (or equivalent Vitamin K antagonist) to keep the International Normalization Ratio (INR) in the range of 2-3 or other anti-thrombotic therapy according to hospital guidelines or physician	prophylaxis regimen based on individual subject status.

<table>
<tr><th>Section</th><th>Previous Text</th><th>Revised Text</th><th>Rationale for change</th></tr>
<tr><td></td><td></td><td>preference is acceptable.</td><td></td></tr>
<tr><td>Table 2 Schedule of Assessments Header</td><td>Every 28 days
(4 wks)[b, c]</td><td>Every 28 days
(4 wks)[b, c]
(1st day of each cycle)</td><td>Added clarification that every 28 days visit could be the 1st day of each new cycle.</td></tr>
<tr><td>Table 2 Scheduled of Assessments Header</td><td>Cycle 3 Day 1 and Every 84 days
(16 wks) thereafter</td><td>Cycle 3 Day 1 and Every 84 days
(12 wks) thereafter</td><td>Corrected to reflect that 84 days equals to 12 weeks (not 16 weeks).</td></tr>
<tr><td>Table 2 Schedule of Assessments</td><td><table><tr><th>Procedures</th><th>CR/CRi/ PR confirmation visit</th></tr><tr><td>Bone marrow aspirate, biopsy, peripheral blood slides for Central Pathology Reviewer[o]</td><td>X[o]</td></tr></table></td><td><table><tr><th>Procedures</th><th>CR/CRi/ PR confirmation visit</th></tr><tr><td>Bone marrow aspirate, biopsy, peripheral blood slides[p]</td><td>X[p]
(CR/CRi only)</td></tr></table></td><td>Although specified in the respective footnote, “CR/CRi only” was added to the table to clarify that this assessment is only required for a CR/CRi confirmation visit, not PR confirmation visit.

The “for Central Pathology Reviewer” was deleted from the procedure name to avoid confusion. In addition to submission of samples for central pathology review, local pathology review of the bone marrow aspirate and biopsy samples is also</td></tr>
</table>

<table>
<tr><th>Section</th><th>Previous Text</th><th>Revised Text</th><th>Rationale for change</th></tr>
<tr><td></td><td></td><td></td><td>required.</td></tr>
<tr><td>Table 2 Schedule of Assessments</td><td><table><tr><th>Procedures</th><th>CR/CRi/ PR confirmation visit</th></tr><tr><td>MRD evaluation[q]</td><td>X[q]</td></tr></table></td><td><table><tr><th>Procedures</th><th>CR/CRi/ PR confirmation visit</th></tr><tr><td>MRD evaluation[r]</td><td>X[r] (CR/CRi only)</td></tr></table></td><td>Although specified in the respective footnote, “CR/CRi only” was added to the table to clarify that this assessment is only required for a CR/CRi confirmation visit, not PR confirmation visit.</td></tr>
<tr><td>Table 2 Schedule of Assessments</td><td><table><tr><th>Procedures</th><th>CR/CRi/ PR confirmation visit</th></tr><tr><td></td><td>X[o]</td></tr></table></td><td><table><tr><th>Procedures</th><th>CR/CRi/ PR confirmation visit</th></tr><tr><td></td><td>X[p] (CR/CRi only)</td></tr></table></td><td>Although specified in the respective footnote, “CR/CRi only” was added to the table to clarify that this assessment is only required for CR/CRi confirmation visit, not PR confirmation visit.</td></tr>
<tr><td>Table 2 Schedule of Assessments (footnote i)</td><td>i. ECG will be performed and interpreted locally. After the screening ECG, the next ECG will be done at Cycle 3 Day 1, and then every 16 weeks while on study drug, and at treatment discontinuation</td><td>i. ECG will be performed and interpreted locally. After the screening ECG, the next ECG will be done at Cycle 3 Day 1, and then every 12 weeks while on study drug, and at treatment discontinuation</td><td>Corrected interval for follow-up ECG assessment per the correction to reflect 84 days equals to 12 weeks (not 16 weeks).</td></tr>
<tr><td>Table 2 Schedule of Assessments (footnote</td><td>k. Hematology includes WBC, HGB, HCT, MCV, differential, platelet count, ANC, ALC, prolymphocyte and reticulocyte count.</td><td>k. Hematology: Central lab assessments includes WBC, RBC, HGB, HCT, MCV, differential, platelet count, ANC, ALC, prolymphocyte and reticulocyte count.</td><td>Added details to clarify required central versus local clinical laboratory</td></tr>
</table>

Section	Previous Text	Revised Text	Rationale for change
k)		Local lab assessments include HGB, ANC, ALC and platelet count. At screening, subject must meet eligibility criteria based on central lab results. At Study Day 1, subject must meet eligibility criteria based on local or central lab results prior to initiating study therapy	assessments.
Table 2 Schedule of Assessments (footnote l)	l. Chemistry includes sodium, potassium, chloride, CO_2, calcium, magnesium, phosphorus, BUN, creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, AST/SGOT, ALT/SGPT, LDH, and uric acid.	l. Chemistry: Central lab assessments includes sodium, potassium, chloride, CO_2, calcium, magnesium, phosphorus, BUN, creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, AST/SGOT, ALT/SGPT, LDH, and uric acid. Local lab assessments include potassium, calcium, phosphorus, creatinine, total bilirubin, AST/SGOT, ALT/SGPT, and uric acid. At screening, subject must meet eligibility criteria based on central lab results. At Study Day 1, subject must meet eligibility criteria based on local or central lab results prior to initiating study therapy.	Added details to clarify required central versus local clinical laboratory assessments.
Table 2 Schedule of Assessments	NA	Footnote added: m. Urinalysis: Local and central assessments will include ketones, sediments and specific gravity.	Added details to clarify required central versus local clinical laboratory assessments.
Table 2 Schedule of Assessments	Original footnote lettering: m, n, o , p, q, r, s, t, u, v, w, x, y, z, aa, bb, cc, dd	Updated respective footnote lettering n, o, p, q, r, s, t, u, v, w, x, y, z, aa, bb, cc, dd, ee	Required due to addition of footnote "m"
Table 2 Schedule of Assessments (previous	n. TSH (thyroid-stimulating hormone), T3, and T4 levels will be assessed at screening, Cycle 3 Day 1 and every 16	o. TSH (thyroid-stimulating hormone), free T3, and free T4 levels will be assessed at screening, Cycle 3 Day 1 and every 12	Corrected interval for follow-up TSH

Section	Previous Text	Revised Text	Rationale for change
footnote n, revised footnote o)	weeks while on study drug and at treatment discontinuation.	weeks while on study drug and at treatment discontinuation. All samples will be analyzed centrally.	assessment per correction to reflect 84 days equals to 12 weeks (not 16 weeks).
Table 2 Schedule of Assessments (previous footnote o, revised footnote p)	o. …Local pathology results for the bone marrow and aspirate sample will also be captured on the eCRFs…	p. ….All bone marrow and aspirate sample will also be analyzed locally and this data will be captured on the eCRFs….	Updated section of footnote to further clarify that the bone marrow aspirate and biopsy need to be analyzed locally, in addition to being submitted for central pathology review.
Table 2 Schedule of Assessments (previous footnote v, revised footnote w)	v. Peripheral blood samples will be collected for these exploratory analyses at specified timepoints. ZAP-70 expression by flow cytometry.	w. Blood samples for β2M, ZAP-70, V_H mutational status will be collected at screening. ZAP-70 expression by flow cytometry.	Updated footnote to specify timepoints for these exploratory assessments. Added statement to clarify these assessments will be analyzed centrally.
Table 2 Schedule of Assessments (previous footnote w, revised footnote x)	w. FISH studies for cytogenetic assessment (CCND1/IgH fusion, 11q, 17 p, 13 q, and Trisomy 12) will be collected at screening	x. Blood sample for FISH studies for cytogenetic assessment (CCND1/IgH fusion, 11q, 17 p, 13 q, and Trisomy 12) will be collected at screening. All samples will be analyzed centrally.	Updated footnote to make it consistent with other exploratory assessments footnotes. Added statement to clarify these assessments will be

Section	Previous Text	Revised Text	Rationale for change
			analyzed centrally.
Table 2 Schedule of Assessments (Previous footnotes, p, q, x, y, z, aa, bb, dd,) (Revised footnotes q, r, y, z, aa, bb, cc, ee)	NA	In footnotes for each of these assessments, the following statement was added "All samples will be analyzed centrally" • [redacted] • MRD evaluation[r] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • PK analysis[ee]	Added statement to clarify these assessments will be analyzed centrally.
Table 2 Schedule of Assessments (previous footnote cc, revised	[redacted]	[redacted]	Since it is possible that a subject may experience tumor flare reaction multiple times during

Section	Previous Text	Revised Text	Rationale for change
footnote dd) 14.3. Assessment of Exploratory Biomarkers			the study, this was updated to specify a maximum number of lymph node biopsies that may be performed for any one subject enrolled into the lymph node biopsy sub-study.
12.2. Methods and Timing of Efficacy Assessments	NA	The average dose of radiation exposure for a subject during CT scan of neck, chest, abdomen and pelvis is approximately 20 mSv for a 70 kg patient. However, the actual amount of radiation exposure for each subject will vary depending on, but not limited to, the size of the subject and type of CT equipment used for the assessment.	Added the average dose of radiation exposure per CT Scan as this information may be required by Ethic Committees/ Institutional Review Boards (ECs/IRBs).
12.2. Methods and Timing of Efficacy Assessments	**Evaluation of MRD status** MRD status will be evaluated for those subjects who reach CR or CRi. A peripheral blood and bone	**Evaluation of MRD status** MRD status will be evaluated for those subjects who reach CR or CRi. A peripheral blood and bone	Added statement to clarify these assessments will be analyzed centrally.

Section	Previous Text	Revised Text	Rationale for change
	marrow aspirate sample will be collected for MRD analysis by flow cytometry at the CR/CRi confirmation visit.	marrow aspirate sample will be collected for MRD analysis by flow cytometry at the CR/CRi confirmation visit. The MRD samples will be analyzed by a central laboratory.	
13. ASSESSMENT OF SAFETY 13.1. Assessments	• Clinical laboratory evaluations: – Hematology: white blood cell (WBC), hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), differential, platelet count, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), prolymphocyte and reticulocyte count – Blood chemistry: sodium, potassium, chloride, CO_2, calcium, magnesium, phosphorus, BUN, creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, AST/SGOT, ALT/SGPT, LDH, and uric acid – Urine analysis – Thyroid functions: TSH, T3 and T4 – Direct antiglobulin test (at screening only) • Calculated (method of Cockroft-Gault) creatinine clearance	• The following clinical laboratory assessments will be analyzed centrally: – Hematology: white blood cell (WBC), red blood cell (RBC), hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), differential, platelet count, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), prolymphocyte and reticulocyte count – Blood chemistry: sodium, potassium, chloride, CO_2, calcium, magnesium, phosphorus, BUN, creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, AST/SGOT, ALT/SGPT, LDH, and uric acid – Urinalysis: ketones, sediments and specific gravity – Thyroid functions: TSH, free T3 and free T4	Added details to clarify required central versus local clinical laboratory assessments.

Section	Previous Text	Revised Text	Rationale for change
	(creatinine clearance may also be obtained by the 24-hour collection method at the investigator's discretion)	– Direct antiglobulin test (at screening only) – Calculated (method of Cockroft-Gault) creatinine clearance (creatinine clearance may also be obtained by the 24-hour collection method at the investigator's discretion) – At screening, subject must meet eligibility criteria based on central lab results. At Study Day 1, subject must meet eligibility criteria based on local or central lab results prior to initiating study therapy. • The following clinical laboratory assessments will be analyzed locally: – Hematology: hemoglobin (HGB), platelet count, absolute neutrophil count (ANC), absolute lymphocyte count (ALC) – Blood chemistry: potassium, calcium, phosphorus, creatinine, total bilirubin, AST/SGOT, ALT/SGPT and uric acid – Urinalysis: ketones, sediments and specific gravity	

Section	Previous Text	Revised Text	Rationale for change
		– Calculated (method of Cockroft-Gault) creatinine clearance (creatinine clearance may also be obtained by the 24-hour collection method at the investigator's discretion) – At screening, subject must meet eligibility criteria based on central lab results. At Study Day 1, subject must meet eligibility criteria based on local or central lab results prior to initiating study therapy.	
14.2. Assessment of Pharmacokinetics	Pharmacokinetic assessments will be performed in up to 40 subjects who provide additional consent at select centers. Both intensive and sparse PK blood sampling will be performed in these subjects.	Pharmacokinetic assessments will be performed in up to 40 subjects who provide additional consent at select centers. Both intensive and sparse PK blood sampling will be performed in these subjects. All PK samples will be analyzed centrally.	Added statement to clarify these assessments will be analyzed centrally.
14.3. Assessment of Exploratory Biomarkers	• Peripheral blood samples for Beta-2 Microglobulin (β2M), FISH analyses (CCND1/IgH fusion, del 11q, del 17 p, del 13 q, and Trisomy 12), ZAP-70 expression, V_H mutational status assessment,	• Peripheral blood samples for Beta-2 Microglobulin (β2M), FISH analyses (CCND1/IgH fusion, del 11q, del 17 p, del 13 q, and Trisomy 12), ZAP-70 expression, V_H mutational status assessment, and	Added statement to clarify these assessments will be analyzed centrally.

Section	Previous Text	Revised Text	Rationale for change
	ZAP-70 expression by flow cytometry) will be collected at screening.	ZAP-70 expression by flow cytometry) will be collected at screening. The samples will be analyzed centrally.	

Section	Previous Text	Revised Text	Rationale for change

Section	Previous Text	Revised Text	Rationale for change