PHASE 1/2 STUDY TO DETERMINE THE SAFETY, PHARMACOKINETICS, AND EFFICACY OF SINGLE AGENT CC-122 AND THE COMBINATIONS OF CC-122 AND IBRUTINIB AND CC-122 AND OBINUTUZUMAB IN SUBJECTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

INVESTIGATIONAL PRODUCT (IP):	**CC-122**
PROTOCOL NUMBER:	**CC-122-CLL-001**
DATE FINAL:	**15 October 2014**
AMENDMENT No. 1:	**26 November 2014**
AMENDMENT No. 2:	**16 February 2015**
AMENDMENT No. 3:	**30 April 2015**
AMENDMENT No. 4:	**27 August 2015**
AMENDMENT No. 5:	**28 March 2016**
AMENDMENT No. 6:	**06 June 2017**
AMENDMENT No. 7:	**27 July 2018**
EudraCT NUMBER:	**2014-003056-31**
IND NUMBER:	**111489**
SPONSOR NAME / ADDRESS:	[redacted]

MEDICAL MONITOR / EMERGENCY CONTACT INFORMATION

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

{See appended electronic signature page}
Signature of Celgene Therapeutic Area Head **dd mmm yyyy**
[redacted]
Printed Name of Celgene Therapeutic Area Head and Title
By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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

COORDINATING PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Coordinating Principal Investigator	**dd mmm yyyy**
Printed Name of Coordinating Principal Investigator **Institution Name:**_____ By my signature, I agree the protocol has been written to comply with ICH Good Clinical Practices guidelines and agree to offer guidance throughout the study as needed.	

PROTOCOL SUMMARY

On 05 Jul 2018, Celgene informed all study sites that further development of CC-122 in Chronic Lymphocytic Leukemia (CLL) will be discontinued after completion of the current Phase 1 Dose Escalation Phase. Enrollment into the Phase 2 Dose Expansion Phase will not proceed forward as originally planned. The decision was not based on adverse safety findings, and no new safety signals for CC-122 have been identified. Subjects already enrolled and who are receiving clinical benefit in the opinion of the treating investigator may continue to receive study treatment up to a maximum of 24 cycles of CC-122 irrespective of treatment arm. Protocol Amendment 7 is issued to provide further guidance regarding study procedures for the remaining patients on study treatment, study closure, and long-term follow-up.

Study Title

Phase 1/2 Study to Determine the Safety, Pharmacokinetics, and Efficacy of Single Agent CC-122 and the Combinations of CC-122 and Ibrutinib and CC-122 and Obinutuzumab in Subjects with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Objectives

As of 05 Jul 2018, enrollment of new subjects into Phase 1 has been discontinued. Subjects already enrolled who are receiving clinical benefit in the opinion of the treating investigator may continue to receive study treatment up to a maximum of 24 cycles of CC-122.

Primary Objectives

- Determine the safety of single agent CC-122 in subjects with relapsed/refractory (R/R) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)
- Determine the safety and tolerability of the combination of CC-122 and ibrutinib and determine the recommended Phase 2 dose (RP2D) of the combination in ibrutinib naïve CLL/SLL subjects
- Determine the safety and tolerability of the combination of CC-122 and obinutuzumab and determine the RP2D of the combination in subjects with R/R CLL/SLL

Secondary Objectives

- Characterize CC-122 pharmacokinetics (PK) in subjects with CLL and assess potential drug-drug interactions when CC-122 is given in combination with ibrutinib or obinutuzumab
- Determine ibrutinib plasma concentrations when given alone or in combination with CC-122
- Determine the preliminary efficacy of single agent CC-122, the combination of CC-122 and ibrutinib, and the combination of CC-122 and obinutuzumab

[redacted]

Study Design

As of 05 Jul 2018, enrollment of new subjects into Phase 1 has been discontinued. Phase 2 will not proceed.

CC-122-CLL-001 is a Phase 1/2, multicenter, open-label, dose finding study to determine the safety, PK, and preliminary efficacy of CC-122 administered orally to subjects with CLL/SLL.

The following will be evaluated:

- **Arm A:** CC-122 single agent
- **Arm B:** CC-122 in combination with ibrutinib
- **Arm C:** CC-122 in combination with obinutuzumab

The Dose Escalation Phase (Phase 1) will be comprised of an intrasubject dose escalation cohort for single agent CC-122 (Arm A) in parallel with ascending fixed-dose cohorts of the combinations of CC-122 and ibrutinib (Arm B) and CC-122 and obinutuzumab (Arm C) evaluated using a 3 + 3 design to determine the not tolerated dose (NTD) and maximum tolerated dose (MTD).

Up to approximately 20 subjects will be evaluated in the intrasubject dose escalation cohort in Arm A and three to six subjects will be evaluated in each fixed-dose cohort in Arms B and C; therefore, approximately 68 (46-92) subjects are anticipated to be enrolled in Phase 1. The final number of subjects will depend on the number of dose levels tested and the number of dose limiting toxicities (DLTs) observed within each cohort.

For Arm A, subjects will receive a starting dose of 1.0 mg, and may dose escalate every 2 weeks in 0.5 mg increments, based on subject tolerability at the discretion of the investigator. For Arms B and C, a safety review committee (SRC) whose members include the sponsor's medical monitor, drug safety physician, and a subset of investigators, will determine a preliminary RP2D for each combination treatment arm based on an integrated assessment of the safety, available PK and pharmacodynamic data, and preliminary efficacy information. For the fixed-dose cohorts, the SRC will make the recommendation of whether to open the next dose cohort and the incremental increase in dose (ie, 0.5 or 1.0 mg) after review of the safety data of the current dose cohort (after full enrollment and completion of the DLT evaluation period). The 1.0 mg increment is allowed only after the first two dose cohorts of 0.5 and 1.0 mg have been completed.

After completion of the fixed-dose cohorts in Arms B and C, the SRC will make the determination whether to evaluate an additional intrasubject dose escalation cohort per each

combination treatment arm. The starting dose will be determined by the SRC, with intrasubject dose escalation up to a maximum dose of 4.0 mg.

If in the event higher doses of CC-122 are shown to be safe in other hematologic malignancies in ongoing CC-122 studies, the maximum dose of 4.0 mg may be increased after approval by the SRC.

Once the RP2D is established for Arms B and C, an expansion cohort per arm may be opened in the Dose Expansion Phase (Phase 2) to further evaluate the safety and efficacy of CC-122 in combination with ibrutinib and/or CC-122 in combination with obinutuzumab:

Arm B (CC-122 in combination with ibrutinib) (N = 50):

- Expansion Cohort 1: Subjects who are ibrutinib-naïve and have high-risk CLL (see Section 7.2)
  - Treatment-naïve (TN) CLL (N = 10)
  - R/R CLL (N = 40)

Arm C (CC-122 in combination with obinutuzumab) (N = 40):

- Expansion Cohort 2: CLL subjects who are B-cell receptor pathway inhibitor (BCR PI) or venetoclax failures (see Section 7.2)

In total, approximately 90 subjects are anticipated to enroll in the Dose Expansion Phase.

All active subjects who are receiving clinical benefit in the opinion of the treating investigator may continue to receive study treatment up to a maximum of 24 cycles of CC-122, or until disease progression (PD), unacceptable toxicity, or discontinuation for any other reason, whichever is earlier. Subjects who achieve minimal residual disease (MRD) negativity (in both peripheral blood and bone marrow) lasting for a minimum of 3 months in duration have the option to discontinue study treatment; study treatment in these subjects may be resumed at the time of MRD positivity (Section 4.1 for additional details).

Study Population

The study population consists of Dose Escalation Phase (Phase 1) subjects who were enrolled under previous amendments and were ongoing during Amendment 6, dated 06 Jun 2017. As of 05 Jul 2018, enrollment of new subjects into Phase 1 has been discontinued and Phase 2 will not proceed.

Eligible subjects include those with CLL/SLL requiring treatment as defined by the modified International Workshop on Chronic Lymphocytic Leukemia (IWCLL) Guidelines for the Diagnosis and Treatment of CLL [redacted]

For Arms A and C, subjects must have received at least one prior treatment which must include chemoimmunotherapy or an approved Bruton's tyrosine kinase (BTK) inhibitor unless co-morbidity or contraindication precludes such a therapy.

For Arm B, subjects must not have received prior ibrutinib treatment (ie, ibrutinib naïve) or any BTK inhibitor. During the Expansion Phase, subjects must also possess high-risk features.

Please refer to Section 7.2 for additional details regarding study population for each treatment arm.

Length of Study

The study is expected to last approximately 5 years and will consist of three phases: Screening, Treatment, and Follow-up.

During the Screening Phase, lasting up to 28 days from the time of signing informed consent to first dose administered, subjects will undergo assessments to determine their eligibility.

Subjects who qualify for enrollment into the study will enter the Treatment Phase, during which subjects will receive investigational product(s) [IP(s)] at a predetermined dose and schedule until the underlying CLL/SLL has progressed or the subject has discontinued IP treatment for unacceptable toxicity or other reasons.

Subjects enrolled as of 05 Jul 2018 who are receiving clinical benefit in the opinion of the treating investigator may continue to receive study treatment up to a maximum of 24 cycles of CC-122 irrespective of treatment arm.

The Follow-up Phase will begin at study treatment discontinuation. Subjects will have a visit at the end of treatment as soon as possible once IP has been discontinued and at 28 days after the last dose of IP. All subjects discontinued for any reason other than progressive disease, withdrawal of consent, or death, will be contacted every 90 days following the date of the 28-day follow-up visit for information regarding the status of their disease and for the type and start date for any subsequent anticancer therapy. Efficacy assessments (including clinical, laboratory tests, and CT scans as indicated in the Tables of Events, Table 3 through Table 5) will continue until documented PD or initiation of subsequent anti-CLL therapy.

The End of Trial is defined as either the date of the last visit of the last subject to complete the study, or the date of receipt of the last data point from the last subject that is required for primary, secondary, and/or exploratory analysis, as pre-specified in the protocol and/or the statistical analysis plan (SAP), whichever is the later date.

Overview of Efficacy Assessments

- Best overall response [complete response (CR), complete response with incomplete marrow recovery (CRi), nodular partial response (nPR), partial response (PR), partial response with lymphocytosis (PRL) (applicable to Arm B only)] as assessed by the International Working Group Criteria [redacted] with modifications
- Clinical laboratory evaluations
- Tumor imaging assessment (CT scan)
- Bone marrow aspirate/biopsy
- MRD assessment (peripheral blood and bone marrow aspirate)
- Performance status
- B-Symptom evaluation

Overview of Safety Assessments

- Adverse events using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03
- Vital signs
- Physical examination
- Electrocardiogram (ECG)
- Clinical laboratory assessments
- Left ventricular ejection fraction (LVEF)
- Cardiac laboratory testing
- Ophthalmology examination

[redacted]

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1. INTRODUCTION

Please refer to the most current version of the CC-122 Investigator's Brochure (IB), the obinutuzumab IB, the package inserts (PI) for ibrutinib (IMBRUVICA®) and obinutuzumab (GAZYVA®), and the Summary of Product Characteristics (SmPC) for ibrutinib (IMBRUVICA) and obinutuzumab (GAZYVARO®) for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of the respective agents.

2. STUDY OBJECTIVES

2.1. Primary Objectives

The primary objectives of the study are:

- Determine the safety of single agent CC-122 in subjects with R/R CLL/SLL
- Determine the safety and tolerability of the combination of CC-122 and ibrutinib and determine the RP2D of the combination in ibrutinib-naive CLL/SLL subjects
- Determine the safety and tolerability of the combination of CC-122 and obinutuzumab and determine the RP2D of the combination in subjects with R/R CLL/SLL

2.2. Secondary Objectives

The secondary objectives of the study are:

- Characterize CC-122 PK in subjects with CLL and assess potential drug-drug interactions when CC-122 is given in combination with ibrutinib or obinutuzumab
- Determine ibrutinib plasma concentrations when given alone or in combination with CC-122
- Determine the preliminary efficacy of single agent CC-122, the combination of CC-122 and ibrutinib, and the combination of CC-122 and obinutuzumab

3. STUDY ENDPOINTS

3.1. Primary Endpoints

- Incidence and severity of adverse events using the NCI CTCAE criteria (version 4.03), including DLTs
- CC-122 in combination with ibrutinib and CC-122 in combination with obinutuzumab: Determination of the NTD and MTD

3.2. Secondary Endpoints

- CC-122 plasma concentrations when administered alone or in combination with ibrutinib or obinutuzumab
- CC-122 pharmacokinetic parameters when administered in combination with ibrutinib
- Ibrutinib plasma concentrations and/or pharmacokinetic parameters when administered in combination with CC-122
- Best overall response [CR, CRi, nPR, PR, PRL (applicable to Arm B only)]
- MRD negativity rate
- Duration of response (DoR)
- Progression-free survival (PFS)

4. OVERALL STUDY DESIGN

4.1. Study Design

As of 05 Jul 2018, enrollment of new subjects into Phase 1 has been discontinued. Phase 2 will not proceed.

CC-122-CLL-001 is a Phase 1/2, multicenter, open-label, dose finding study to determine the safety, PK, and preliminary efficacy of CC-122 administered orally to subjects with CLL/SLL. The following will be evaluated:

- **Arm A:** CC-122 single agent
- **Arm B:** CC-122 in combination with ibrutinib
- **Arm C:** CC-122 in combination with obinutuzumab

The Dose Escalation Phase (Phase 1) will be comprised of an intrasubject dose escalation cohort for single agent CC-122 (Arm A) in parallel with ascending fixed-dose cohorts of the combinations of CC-122 and ibrutinib (Arm B) and CC-122 and obinutuzumab (Arm C) evaluated using a 3 + 3 design to determine the NTD and MTD.

Up to approximately 20 subjects will be evaluated in the intrasubject dose escalation cohort in Arm A and three to six subjects will be evaluated in each fixed-dose cohort in Arms B and C; therefore, approximately 68 (46-92) subjects are anticipated to be enrolled in Phase 1. The final number of subjects will depend on the number of dose levels tested and the number of DLTs observed within each cohort.

For Arm A, subjects will receive a starting dose of 1.0 mg, and may dose escalate every 2 weeks in 0.5 mg increments, based on subject tolerability at the discretion of the investigator. For Arms B and C, an SRC whose members include the sponsor's medical monitor, drug safety physician, and a subset of investigators, will determine a preliminary RP2D for each combination treatment arm based on an integrated assessment of the safety, available PK and pharmacodynamic data, and preliminary efficacy information. For the fixed-dose cohorts, the SRC will make the recommendation of whether to open the next dose cohort and the incremental increase in dose (ie, 0.5 or 1.0 mg) after review of the safety data of the current dose cohort (after full enrollment and completion of the DLT evaluation period). The 1.0 mg increment is allowed only after the first two dose cohorts of 0.5 and 1.0 mg have been completed.

After completion of the fixed-dose cohorts in Arms B and C, the SRC will make the determination whether to evaluate an additional intrasubject dose escalation cohort per each combination treatment arm. The starting dose will be determined by the SRC, with intrasubject dose escalation up to a maximum dose of 4.0 mg.

If in the event higher doses of CC-122 are shown to be safe in other hematologic malignancies in ongoing CC-122 studies, the maximum dose of 4.0 mg may be increased after approval by the SRC.

Once the RP2D is established for Arms B and C, an expansion cohort per arm may be opened in the Dose Expansion Phase (Phase 2) to further evaluate the safety and efficacy of CC-122 in combination with ibrutinib and/or CC-122 in combination with obinutuzumab:

Arm B (CC-122 in combination with ibrutinib) (N = 50):

- Expansion Cohort 1: Subjects who are ibrutinib-naïve and have high-risk CLL (see Section 7.2)
  - TN CLL (N = 10)
  - R/R CLL (N = 40)

Arm C (CC-122 in combination with obinutuzumab) (N = 40):

- Expansion Cohort 2: CLL subjects who are BCR PI or venetoclax failures (see Section 7.2)

In total, approximately 90 subjects are anticipated to enroll in the Dose Expansion Phase.

All active subjects who are receiving clinical benefit in the opinion of the treating investigator may continue to receive study treatment up to a maximum of 24 cycles of CC-122, or until PD, unacceptable toxicity or discontinuation for any other reason, whichever is earlier. Subjects who achieve MRD negativity (in both peripheral blood and bone marrow) lasting for a minimum of 3 months in duration have the option to discontinue study treatment, with subsequent MRD tests follow-up (in peripheral blood and/or bone marrow) every 3 cycles for the first year, and every 6 cycles thereafter. Study treatment in these subjects may be resumed at the time of MRD positivity (either in peripheral blood or bone marrow).

Dose Escalation Phase:

As of 05 Jul 2018, enrollment of new subjects into Phase 1 has been discontinued.

The Dose Escalation Phase will be comprised of an intrasubject dose escalation cohort for single agent CC-122 (Arm A) in parallel with ascending fixed-dose cohorts of the combinations of CC-122 and ibrutinib (Arm B), and CC-122 and obinutuzumab (Arm C), evaluated using a 3 + 3 design:

Arm A (CC-122 single agent):

An intrasubject dose escalation cohort of CC-122 starting at the 1.0 mg dose level up to a maximum of 4.0 mg will be evaluated.

In the event higher doses of CC-122 are shown to be safe in other hematologic malignancies in ongoing CC-122 studies, the maximum dose of 4.0 mg may be increased after approval by the SRC.

Each subject will be permitted to dose escalate by 0.5 mg increments every 2 weeks based on investigator assessment of the individual subject's tolerability (ie, escalation to the next dose level requires no DLT or dose reduction at the current dose level in addition to meeting the criteria outlined in Section 8.2.8).

However, dose escalation per cycle is not mandatory if the subject is benefiting (ie, objective evidence of disease response based on absolute lymphocyte count [ALC] reduction or shrinkage in measurable lesions required) from their current dose in the absence of significant toxicities. Subjects who are enrolled to fixed dose cohorts (0.25 mg or 0.5 mg) in Arm A under earlier protocol amendments (ie, protocol amendment 3 or 4) will be allowed to undertake intrasubject dose escalations as described above.

Subjects in Arm A will have the option to receive the addition of ibrutinib or obinutuzumab if there is evidence of PD while on CC-122 monotherapy after the completion of the DLT evaluation and CC-122 in combination with these standard agents has been demonstrated to be safe in the context of this trial. These subjects will receive a maximum of 24 cycles of CC-122 (including prior CC-122 monotherapy). The dose of CC-122 may need to be decreased to the level that has been shown to be safe in Arms B or C per the SRC (ie, < 2 DLTs/6 subjects). Subsequent intrasubject escalation is allowed if higher doses of CC-122 have been deemed tolerable in Arms B or C. This option will also apply to subjects that have enrolled in Arm A prior to IRB/EC approval of Amendment 5 after discussion with the Sponsor Medical Monitor.

CC-122 will be administered starting on Cycle 1 Day 1 on a 5/7-day schedule (5 continuous days out of 7 days per week) up to a maximum of 24 cycles, or until disease progression, unacceptable toxicity, or discontinuation for any other reason, whichever is earlier. Each cycle consists of 28 days.

Subjects will be observed for early DLTs in Cycle 1 (DLT evaluation period). Monitoring for late toxicities necessitating dose reductions or discontinuations will be conducted during Cycles 2 through 6.

Arm B (CC-122 + ibrutinib):

The following arm will be evaluated in parallel to Arm A:

Ascending fixed-dose cohorts of CC-122 starting at 0.5 mg up to a maximum of 4.0 mg or NTD, whichever occurs first, in combination with ibrutinib will be evaluated. After completion of the 0.5 and 1.0 mg fixed-dose cohorts, subsequent cohorts will be allowed to escalate in either 0.5 mg or 1.0 mg increments. Escalation to the next dose level requires 0/3 or ≤ 1/6 DLTs at the current dose level. Further, an escalation increment of 1.0 mg requires the absence of any Grade 3 drug related non-hematologic AEs, any Grade 4 hematological event, and TLS or TFR of any grade at the current dose level. The SRC will make the recommendation of whether to open the next dose cohort and the incremental increase in dose (0.5 or 1.0 mg) after review of the safety data of the current dose cohort (after full enrollment and completion of the DLT evaluation period).

CC-122 will be initiated on Cycle 2 Day 1 and administered on a 5/7-day schedule. Ibrutinib will be administered QD starting on Cycle 1 Day 1 (see Section 8.2 for Treatment Description, Administration and Schedule).

CC-122 and ibrutinib will be administered up to a maximum of 24 cycles of CC-122, or until disease progression, unacceptable toxicity, or discontinuation for any other reason, whichever is earlier. In the event CC-122 is discontinued prior to ibrutinib or if patients have surpassed the 24 cycles of CC-122, Celgene will continue to provide an additional 3 cycles of ibrutinib from the investigational supply to allow time for patients to be switched to commercially available ibrutinib and/or other therapies at the discretion of the treating physician. Subjects will be observed for early DLTs for 28 days following the initiation of CC-122 combination therapy (Cycle 2 Days 1 through 28) (DLT evaluation period). Monitoring for late toxicities necessitating dose reductions or discontinuations will be conducted during the first 6 cycles of combination treatment.

Arm C (CC-122 + obinutuzumab):

The following arm will be evaluated in parallel to Arms A and B:

Ascending fixed-doses cohorts of CC-122 starting at 0.5 mg up to a maximum of 4.0 mg or NTD, whichever occurs first, in combination with obinutuzumab will be evaluated. After completion of the 0.5 and 1.0 mg fixed-dose cohorts, subsequent cohorts will be allowed to escalate in either 0.5 mg or 1.0 mg increments. Escalation to the next dose level requires 0/3 or ≤ 1/6 DLTs at the current dose level. Further, an escalation increment of 1.0 mg requires the absence of any Grade 3 drug related non-hematologic AEs, any Grade 4 hematological event, and TLS or TFR of any grade at the current dose level. The SRC will make the recommendation of whether to open the next dose cohort and the incremental increase (0.5 or 1.0 mg) after review of the safety data of the current dose cohort (after full enrollment and completion of the DLT evaluation period).

CC-122 will be initiated on Cycle 1 Day 9 and administered on a 5/7-day schedule. For subjects on Arm C, Cycle 1 only will consist of 29 days to accommodate the 5/7-day schedule; subsequent cycles will consist of 28 days. Obinutuzumab will be administered intravenously on Cycle 1 Days 1, 2, 8, and 15 (see Section 8.2 for Treatment Description, Administration and Schedule). The dose of obinutuzumab on Day 1 and Day 2 of Cycle 1 may be adjusted per institutional practice provided the combined dose equals 1000 mg. Obinutuzumab will be administered on Day 1 every cycle thereafter up to Cycle 6.

CC-122 will be administered up to a maximum of 24 cycles of CC-122, or until disease progression, unacceptable toxicity, or discontinuation for any other reason, whichever is earlier. In the event CC-122 is discontinued prior to obinutuzumab, Celgene will continue to supply the protocol-specified total of 6 cycles of obinutuzumab. In addition, for patients that have surpassed the 24 cycles of CC-122, Celgene will continue to provide an additional 3 cycles of CC-122 to allow time for patients to be switched to commercially available therapies at the discretion of the treating physician.

Subjects will be observed for early DLTs for 28 days following initiation of CC-122 combination therapy (Cycle 1 Day 9 through Cycle 2 Day 8) (DLT evaluation period). Monitoring for late toxicities necessitating dose reductions or discontinuations will be conducted during Cycles 2 through 6.

Early DLT Evaluation of Intrasubject Dose Escalation Cohort in Arm A:

Up to approximately 20 subjects will be enrolled to Arm A to assess an intrasubject dose escalation schedule for CC-122.

If > 20% (eg, > 4 of 20) of subjects meet the criteria for DLT within 28 days of initial escalation to a dose level, no further intrasubject dose escalation to that dose level will be permitted.

Early DLT Evaluation for Fixed-Dose Cohorts in Arms B and C:

An initial 3 subjects will be enrolled to each of the fixed-dose escalation cohorts in Arms B and C. A dose level will be considered tolerable if 0 of 3 treated subjects experiences a DLT during the DLT evaluation period of each respective group. If 1 of 3 subjects experiences a DLT, 3 additional subjects will be enrolled to that dose level. A dose will be considered the NTD when ≥ 2 out of 6 evaluable subjects in a cohort experience a DLT. If DLTs are observed in ≥ 2 out of

6 evaluable subjects at the first dose level, a lower dose combination may be explored after review of safety data by the SRC (see Section 8.2.1).

After full enrollment and completion of the DLT evaluation period of each dose level, the number and type of DLTs and AEs occurring during the DLT evaluation period will be evaluated. A dose level will be considered tolerated after discussion of these data by the SRC. Subsequent dose cohorts will only be authorized to open for enrollment following a consensus by the SRC. Subjects enrolled in lower CC-122 fixed-dose cohorts will be allowed to escalate immediately to the next higher CC-122 dose level upon SRC approval of the subsequent CC-122 dose. For example, if the SRC has declared the 1.0 mg dose level tolerable and confirmed the opening of the 1.5 or 2.0 mg dose level, the subjects in the lower combination, ie, 0.5 mg CC-122 dose level may escalate to 1.0 mg. The MTD is defined as the highest dose level below the NTD with 0 or 1 of 6 DLT evaluable subjects experiencing a DLT during the specified DLT evaluation period. If only 3 subjects have been enrolled at the last dose level below the NTD, 3 additional subjects will be enrolled. A dose level will be declared the MTD when at least 6 subjects have been enrolled and < 2 subjects have experienced a DLT at that dose level.

An intermediate dose (ie, one between the NTD and the last dose level before the NTD) or additional subjects within any dose cohort may be added to determine the MTD and RP2D more precisely.

Monitoring for Late Toxicities During the Dose Escalation Phase:

Continuous safety monitoring will continue for all cohorts for late toxicities necessitating dose reduction or discontinuation. If at any time during the first 6 cycles of CC-122 treatment > 20% of subjects experience a late toxicity necessitating dose reduction or discontinuation that is clearly not related to disease progression, medical procedure, or intercurrent illness, the dose level will have been considered to exceed the MTD and the RP2D will be selected at a lower dose level. The SRC will be responsible for monitoring these late toxicities and will make the determination that the limit of 20% has been exceeded.

Determination of RP2D:

The SRC will identify a preliminary RP2D for Arms B and C based on an integrated assessment of the safety, available PK and pharmacodynamic data, and preliminary efficacy information.CC-122 data available from other clinical studies will also be considered by SRC. The RP2D selected will not exceed the MTD from the dose escalation cohorts.

Expansion Phase:

As of 05 Jul 2018, Phase 2 will not proceed.

An expansion cohort may be enrolled at each RP2D for Arms B and C for a total of up to 2 expansion cohorts.

During the Expansion Phase of the study, the SRC will continue to review safety data regularly and make recommendations about the study continuation as appropriate. The SRC will monitor for early DLTs (first cycle of CC-122 dosing during CC-122 combination therapy) and will monitor for late toxicities necessitating dose reductions or discontinuations that are clearly not related to disease progression, medical procedure, or intercurrent illness through completion of the first 6 cycles of CC-122 treatment in the expansion cohorts. If at any time the early DLT rate exceeds 20% or the late toxicity rate exceeds 33%, enrollment to that expansion cohort will be

suspended pending evaluation of the safety by the SRC. The SRC may reopen enrollment into that cohort at a lower dose level that has been shown to be tolerated during the dose escalation portion of the study.

The expansion cohorts will be conducted with a futility interim analysis for each cohort as outlined in Section 10.3.1.

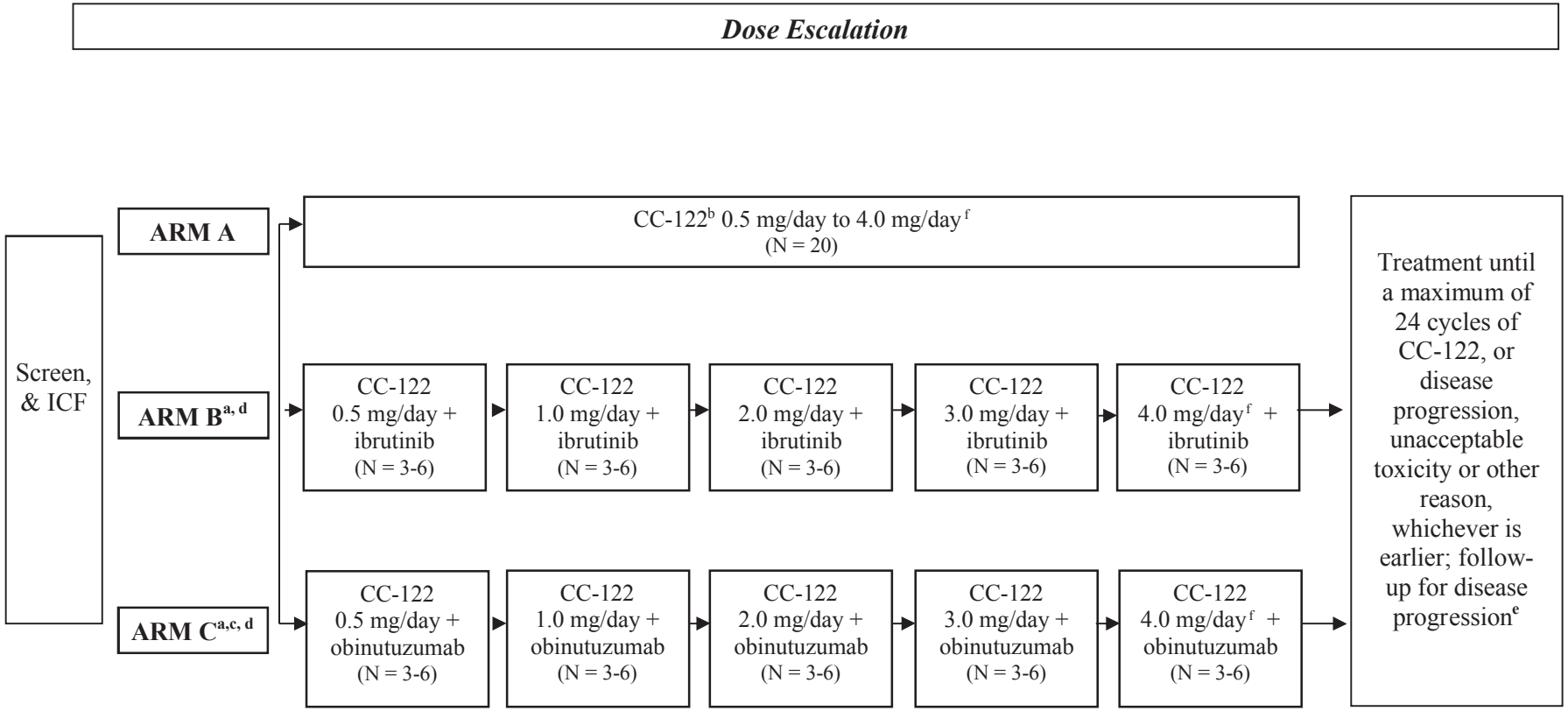
Follow-up Phase:

The Follow-up Phase will begin at study treatment discontinuation. Subjects will have a visit at the end of treatment as soon as possible once IP has been discontinued and at 28 days after the last dose of IP. All subjects discontinued for any reason other than progressive disease, withdrawal of consent, or death, will be contacted every 90 days following the date of the 28-day follow-up visit for information regarding the status of their disease and for the type and start date for any subsequent anticancer therapy. These contacts will typically be via telephone and will not require site visits. Contact will continue until the subject experiences disease progression, starts a new anti-CLL therapy, withdraws consent for further follow-up, or expires.

Efficacy assessments (including clinical, laboratory tests, and CT scans as indicated in the Tables of Events, Table 3 through Table 5) will continue until documented PD or initiation of subsequent anti-CLL therapy.

Figure 5: Overall Study Design

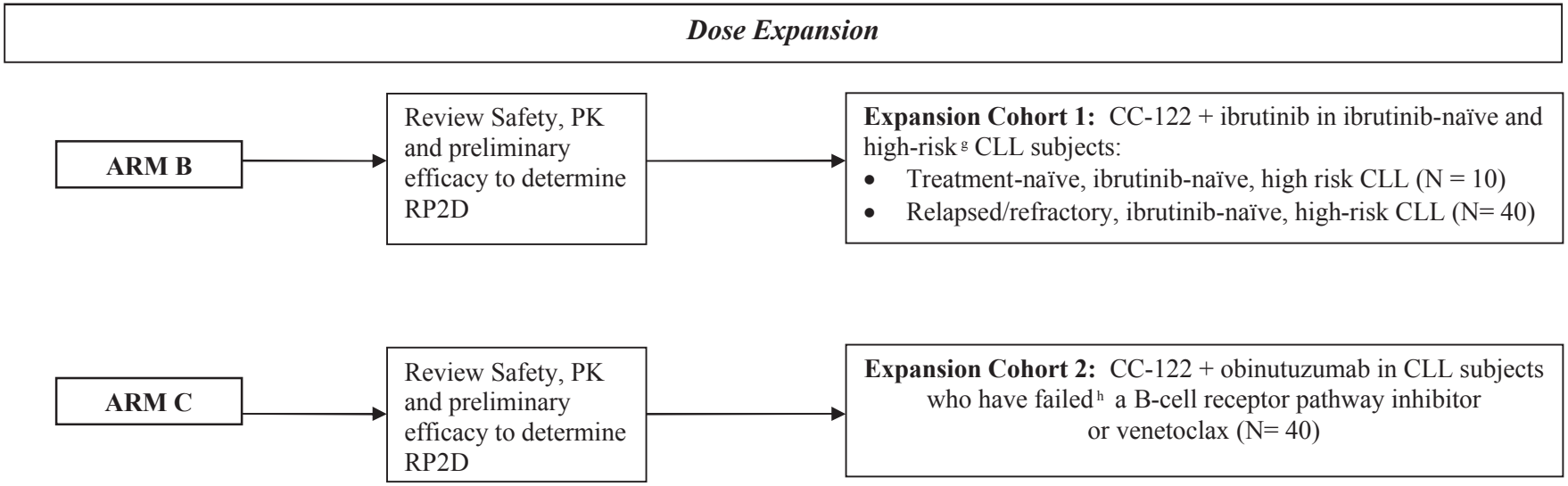
As of 05 Jul 2018, enrollment of new subjects into Phase 1 has been discontinued.



[a] Cohorts will be evaluated using 3+3 dose escalation.
[b] Intrasubject sequential dose escalation by cycle as tolerated; each subject will be permitted to dose escalate each cycle by 0.5 mg increments every 2 weeks based on investigator assessment of the individual subject's tolerability.
[c] Obinutuzumab treatment to Cycle 6 only.
[d] Escalation in 0.5 mg or 1.0 mg increments as determined by the SRC; the 1.0 mg dose increment is allowed following the completion of the 0.5 and 1.0 mg cohorts (see Section 4.1).
[e] Study treatment may be discontinued after MRD negativity has been achieved in both peripheral blood and bone marrow for ≥ 3 months (see Section 4.1).
[f] In the event higher doses of CC-122 are shown to be safe in other hematologic malignancies in ongoing CC-122 studies, the maximum dose of 4.0 mg may be increased after approval by the SRC.

Figure 5: Overall Study Design (Continued)

As of 05 Jul 2018, Phase 2 will not proceed.



[g] High risk definition: TN CLL: 17p-/TP53 mut; R/R CLL: 17p-/TP53 mut., complex karyotype, progression < 24 mo after 1st line CIT
[h] Resistant or intolerant (see detailed definition in Section 7.2).

ICF = Informed Consent Form; PK = Pharmacokinetics; RP2D = Recommended Phase 2 Dose;
CLL = Chronic Lymphocytic Leukemia; SRC = Safety Review Committee; MRD = Minimal Residual Disease.

4.2. Study Duration

The study is expected to last approximately 5 years and will consist of three phases: Screening, Treatment and Follow-up.

During the Screening Phase, lasting up to 28 days from the time of signing informed consent to first dose administered, subjects will undergo assessments to determine their eligibility.

Subjects who qualify for enrollment into the study will enter the Treatment Phase, during which subjects will receive IP at a predetermined dose and schedule until the underlying CLL has progressed or the subject has discontinued IP treatment for unacceptable toxicity or other reasons.

Subjects enrolled as of 05 Jul 2018 and who are receiving clinical benefit in the opinion of the treating investigator may continue to receive study treatment up to a maximum of 24 cycles of CC-122 irrespective of treatment arm.

The Follow-up Phase will begin at study treatment discontinuation.

4.3. End of Trial

The End of Trial is defined as either the date of the last visit of the last subject to complete the study, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as prespecified in the protocol and/or the SAP, whichever is the later date.

5. TABLE OF EVENTS

Table 3: Table of Events – Arm A – CC-122 Single Agent

(As of 05 Jul 2018, enrollment of new subjects into Phase 1 has been discontinued; the procedures below apply to subjects continuing in the study.)

Tests and Observations	Screening	Cycle 1 and the first Cycle of each Dose Escalation[b]			Cycle 2 of each Dose Level[b]		Cycle 3 of each Dose Level[b, o]		≥Cycle 4[b, p]	End of Treatment[b]	Follow-up
	≤ 28 Days Prior to Day 1[a]	Day 1	Days 2 and 4 ± 1 Day	Days 8, 15 and 22 ± 1 Day	Day 1	Days 8, 15 and 22 ± 1 Day	Day 1	Days 8, 15 and 22 ± 1 Day	Day 1		28 days post IP discontinuation
Informed Consent	X	-	-	-	-	-	-	-	-	-	-
Demographics/Medical History	X	-	-	-	-	-	-	-	-	-	-
Physical Examination	X	X	-	-	X	-	X	-	X	X	X
[redacted]	X	-	-	-	-	-	-	-	-	-	-
Vital Signs	X	X	X	X	X	X	X	X	X	X	X
[redacted]	X	X	-	-	X	-	X	-	X	X	X
B-symptoms	X	X	-	-	X	-	X	-	X	X	X
Current Stage/Prognostic Classification	X	-	-	-	-	-	-	-	-	-	-
CBC & Differential	X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry	X	X	X	X	X	X	X	X	X	X	X
Beta-2 Microglobulin	X	-	-	-	-	-	-	-	-	-	-
C-Reactive Protein[m]	X	-	-	X	X	-	X	-	X	-	-
Coagulation	X	X	-	X	X	-	X	-	X	X	-
Urinalysis	X	X	-	-	X	-	X	-	X	X	-

Table 3: Table of Events – Arm A – CC-122 Single Agent (Continued)

	Screening ≤ 28 Days Prior to Day 1[a]	Cycle 1 and the first Cycle of each Dose Escalation[b]			Cycle 2 of each Dose Level[b]		Cycle 3 of each Dose Level[b, o]		≥Cycle 4[b, p]	End of Treatment[b]	Follow-up
	Screen	Day 1	Days 2 and 4 ± 1 Day	Days 8, 15 and 22 ± 1 Day	Day 1	Days 8, 15 and 22 ± 1 Day	Day 1	Days 8, 15 and 22 ± 1 Day	Day 1		28 days post IP discontinuation
Pregnancy Test as specified per PPRMP: (see Section 6.1.14)	X	X	-	X	X	-	X	-	X	X	X
CC-122 Contraceptive and Risk Counseling and Education	To be completed prior to each dispensing of IP as per PPRMP										
HBsAg, anti-HBc, & HCV RNA	X	-	-	-	-	-	-	-	-	-	-
Direct Antiglobulin Test	X	-	-	-	-	-	-	-	-	-	-
Amylase, lipase, fasting lipid profile (eg, cholesterol and triglycerides), creatine kinase, TSH, FT4, LDH, immunoglobulins and T-cell subsets (CD4+, CD8+ and NK cells)	X	X	-	-	X	-	X	-	X	X	-
Troponin-T and BNP	X	X	-	X	X	-	X	-	X	X	-
12-lead ECG	X	X	-	X	X	-	X	-	X	X	-
Ophthalmology Exam[c]	X	-	-	-	-	-	-	-	-	-	-
Cardiac ECHO or MUGA[d]	X	-	-	-	X	-	-	-	X[d]	X	-
Tumor Imaging Assessment[e]	X	-	-	-	-	-	-	-	X[e]	X[e]	-

Table 3: Table of Events – Arm A – CC-122 Single Agent (Continued)

	Screening ≤ 28 Days Prior to Day 1[a]	Cycle 1 and the first Cycle of each Dose Escalation[b]			Cycle 2 of each Dose Level[b]		Cycle 3 of each Dose Level[b, o]		≥Cycle 4[b, p]	End of Treatment[b]	Follow-up
	Screen	Day 1	Days 2 and 4 ± 1 Day	Days 8, 15 and 22 ± 1 Day	Day 1	Days 8, 15 and 22 ± 1 Day	Day 1	Days 8, 15 and 22 ± 1 Day	Day 1		28 days post IP discontinuation
Efficacy Response Assessment [f]	-	-	-	-	-	-	-	-	X[f]	X	-
[redacted]	X	-	-	-	-	-	-	-	-	-	-
Bone Marrow Aspirate/ Biopsy [g]	X	-	-	-	-	-	-	-	X[g]	-	-
Peripheral Blood for MRD Assessment[h]	X	-	-	-	-	-	-	-	X[h]	-	-
[redacted]	X	-	-	-	-	-	-	-	-	-	-
[redacted]	-	X	-	-	-	-	-	-	-	-	-
[redacted]	-	X	-	X[k]	X[k]	X[k]	-	X[k]	-	-	-
Dispense CC-122 [n]	-	X	-	-	X	-	X	-	X	-	-
Drug Accountability/Compliance	-	-	-	-	X	-	X	-	X	X	-
[redacted]	X	X	X	X	X	X	X	X	X	X	X
[redacted]	-	X	X	X	X	X	X	X	X	X	-

Table 3: Table of Events – Arm A – CC-122 Single Agent (Continued)

	Screening ≤ 28 Days Prior to Day 1[a]	Cycle 1 and the first Cycle of each Dose Escalation[b]			Cycle 2 of each Dose Level[b]		Cycle 3 of each Dose Level[b, o]		≥Cycle 4[b, p]	End of Treatment[b]	Follow-up
	Screen	Day 1	Days 2 and 4 ± 1 Day	Days 8, 15 and 22 ± 1 Day	Day 1	Days 8, 15 and 22 ± 1 Day	Day 1	Days 8, 15 and 22 ± 1 Day	Day 1		28 days post IP discontinuation
[redacted]	X	X	X	X	-	-	-	-	-	-	-
Adverse Events	X	X	X	X	X	X	X	X	X	X	X

[redacted]

Please refer to Section 6 for a detailed description of Arm A procedures.

Table 4: Table of Events – Arm B – CC-122 Plus Ibrutinib

(As of 05 Jul 2018, enrollment of new subjects into Phase 1 has been discontinued; the procedures below apply to subjects continuing in the study.)

Tests and Observations	Screening	Cycle 1[b]	Cycle 2[b]			Cycle 3[b]		Cycle 4[b, n]		≥ Cycle 5[b, o]	End of Treatment[b]	Follow-up
	≤ 28 Days Prior to Day 1[a]	Day 1	Day 1	Days 2 and 4 ± 1 Day	Days, 8, 15 and 22 ± 1 Day	Day 1	Day 8, 15 and 22 ± 1 Day	Day 1	Days 8, 15 and 22 ± 1 Day	Day 1		28 days post IP discontinuation
Informed Consent	X	-	-	-	-	-	-	-	-	-	-	-
Demographics/Medical History	X	-	-	-	-	-	-	-	-	-	-	-
Physical Examination	X	X	X	-	-	X	-	X	-	X	X	X
CIRS Score Assessment	X	-	-	-	-	-	-	-	-	-	-	-
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X
ECOG PS	X	X	X	-	-	X	-	X	-	X	X	X
[redacted]	X	X	X	-	-	X	-	X	-	X	X	X
Current Stage/Prognostic Classification	X	-	-	-	-	-	-	-	-	-	-	-
CBC & Differential	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry	X	X	X	X	X	X	X	X	X	X	X	X
Beta-2 Microglobulin	X	-	-	-	-	-	-	-	-	-	-	-
C-Reactive Protein[m]	X	-	-	-	X	X	-	X	-	X	-	-
Coagulation	X	X	X	-	X	X	-	X	-	X	X	-
Urinalysis	X	X	X	-	-	X	-	X	-	X	X	-
Pregnancy Test as specified per PPRMP: (see Section 6.1.14)	X	X	X	-	X	X	-	X	-	X	X	X

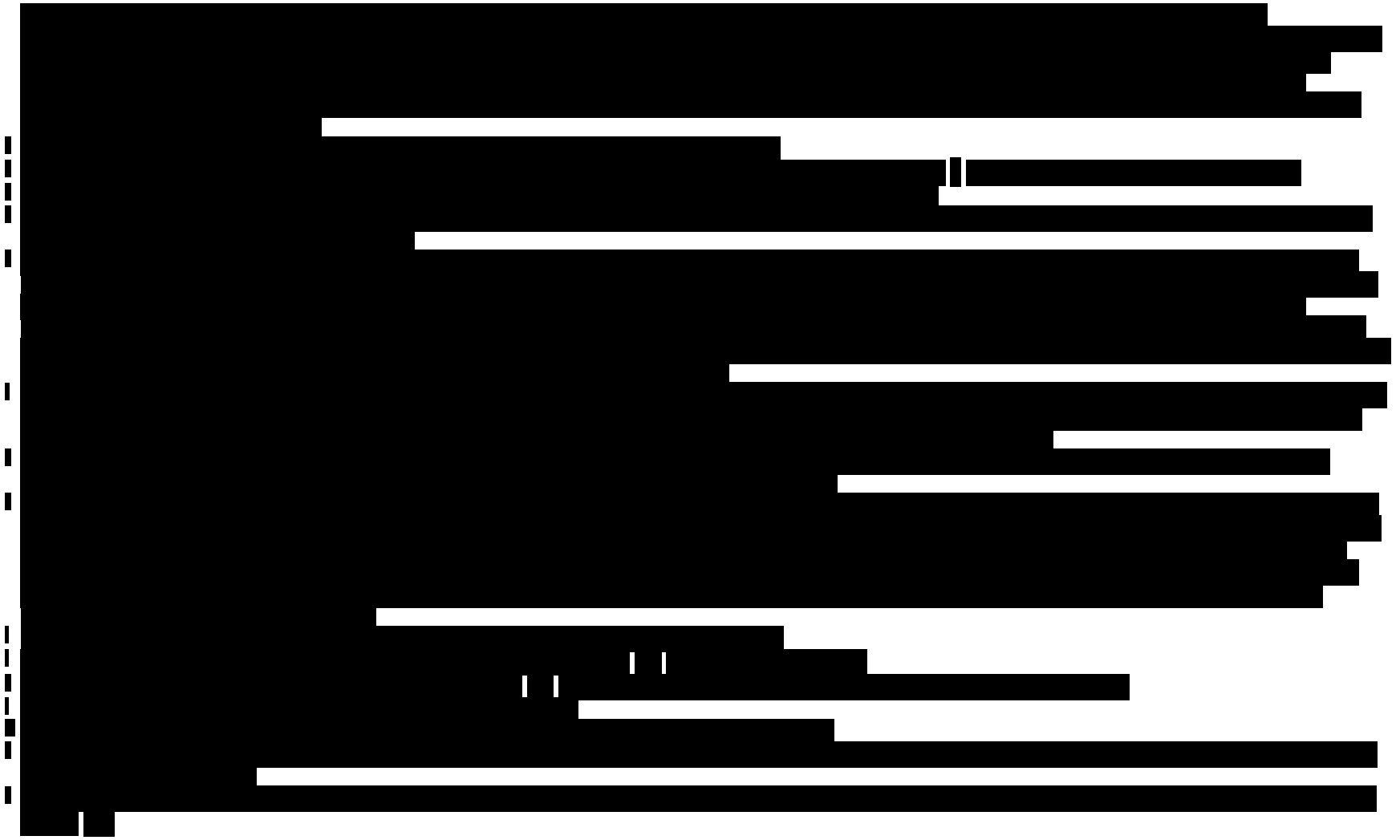
Table 4: Table of Events – Arm B – CC-122 Plus Ibrutinib (Continued)

	Screening ≤ 28 Days Prior to Day 1[a]	Cycle 1[b]	Cycle 2[b]			Cycle 3[b]		Cycle 4[b, n]		≥ Cycle 5[b, o]	End of Treatment[b]	Follow-up
	Screen	Day 1	Day 1	Days 2 and 4 ± 1 Day	Days, 8, 15 and 22 ± 1 Day	Day 1	Day 8, 15 and 22 ± 1 Day	Day 1	Days 8, 15 and 22 ± 1 Day	Day 1		28 days post IP discontinuation
CC-122 Contraceptive and Risk Counseling and Education	To be completed prior to each dispensing of IP as per PPRMP											
HBsAg, anti-HBc, & HCV RNA	X	-	-	-	-	-	-	-	-	-	-	-
Direct Antiglobulin Test	X	-	-	-	-	-	-	-	-	-	-	-
Amylase, lipase, fasting lipid profile (eg, cholesterol and triglycerides), creatine kinase, TSH, FT4, LDH, immunoglobulins and T-cell subsets (CD4+, CD8+ and NK cells)	X	X	X	-	-	X	-	X	-	X	X	-
Troponin-T and BNP	X	-	X	-	X	X	-	X	-	X	X	-
12-lead ECG	X	X	X	-	X	X	-	X	-	X	X	-
Ophthalmology Exam[c]	X	-	-	-	-	-	-	-	-	-	-	-
Cardiac ECHO or MUGA[d]	X	-	-	-	-	X	-	-	-	X[d]	X	-
Tumor Imaging Assessment[e]	X	-	-	-	-	-	-	-	-	X[e]	X[e]	-
Efficacy Response Assessment[f]	-	-	-	-	-	-	-	X[f]	-	X[f]	X	-
[redacted]	X	-	-	-	-	-	-	-	-	-	-	-

Table 4: Table of Events – Arm B – CC-122 Plus Ibrutinib (Continued)

	Screening ≤ 28 Days Prior to Day 1[a]	Cycle 1[b]	Cycle 2[b]			Cycle 3[b]		Cycle 4[b, n]		≥ Cycle 5[b, o]	End of Treatment[b]	Follow-up
	Screen	Day 1	Day 1	Days 2 and 4 ± 1 Day	Days, 8, 15 and 22 ± 1 Day	Day 1	Day 8, 15 and 22 ± 1 Day	Day 1	Days 8, 15 and 22 ± 1 Day	Day 1		28 days post IP discontinuation
Bone Marrow Aspirate/ Biopsy[g]	X[f]	-	-	-	-	-	-	-	-	X[g]	-	-
Peripheral Blood for MRD Assessment[h]	X	-	-	-	-	-	-	-	-	X[h]	-	-
[redacted]	X	-	-	-	-	-	-	-	-	-	-	-
[redacted]	X	-	-	-	-	-	-	-	-	-	X	-
[redacted]	X	-	X[j]	-	X[j]	-	X[j]	X[j]	-	X[j]	-	-
[redacted]	-	X[k]	X[k]	-	X[k]	-	X[k]	-	-	-	-	-
Dispense Ibrutinib	-	X	X	-	-	X	-	X	-	X	-	-
Dispense CC-122	-	-	X	-	-	X	-	X	-	X	-	-
Drug Accountability/Compliance	-	-	X	-	-	X	-	X	-	X	X	-
Concomitant Medications/ Procedures	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]	-	-	X	X	X	X	X	X	X	X	X	-
Allopurinol Administration as Tumor Lysis Prophylaxis[l]	X	X	X	X	X	-	-	-	-	-	-	-
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X

[redacted]



Please refer to Section 6 for a detailed description of Arm B procedures.

Table 5: Table of Events – Arm C – CC-122 Plus Obinutuzumab

(As of 05 Jul 2018, enrollment of new subjects into Phase 1 has been discontinued; the procedures below apply to subjects continuing in the study.)

	Screening	Cycle 1[b, p]							Cycle 2[b]		Cycle 3[b, q]		≥ Cycle 4[b, r]	End of Treatment[b]	Follow-up
Tests and Observations	**≤ 28 Days Prior to Day 1[a]**	**Day 1**	**Day 2**	**Day 4**	**Day 8 ± 1 Day**	**Day 9 ± 1 Day**	**Days 10 and 12 ± 1 Day**	**Days 16 and 23 ± 1 Day**	**Day 1**	**Days 8, 15 and 22 ± 1 Day**	**Day 1**	**Days 8, 15 and 22 ± 1 Day**	**Day 1**		**28 days post IP discontin-uation**
Informed Consent	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Demographics/Medical History	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Physical Examination	X	X	-	-	-	-	-	-	X	-	X	-	X	X	X
[redacted]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]	X	X	-	-	-	-	-	-	X	-	X	-	X	X	X
[redacted]	X	X	-	-	-	-	-	-	X	-	X	-	X	X	X
Current Stage/Prognostic Classification	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CBC & Differential	X	X	X	-	X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Beta-2 Microglobulin	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
C-Reactive Protein[n]	X	-	-	-	X	-	-	X	X	-	X	-	X	-	-
Coagulation	X	X	-	-	X	-	-	X	X	-	X	-	X	X	-
Urinalysis	X	X	-	-	-	-	-	-	X	-	X	-	X	X	-
Pregnancy Test as specified per PPRMP: (see Section 6.1.14)	X	X	-	-	X	-	-	X	X	-	X	-	X	X	X

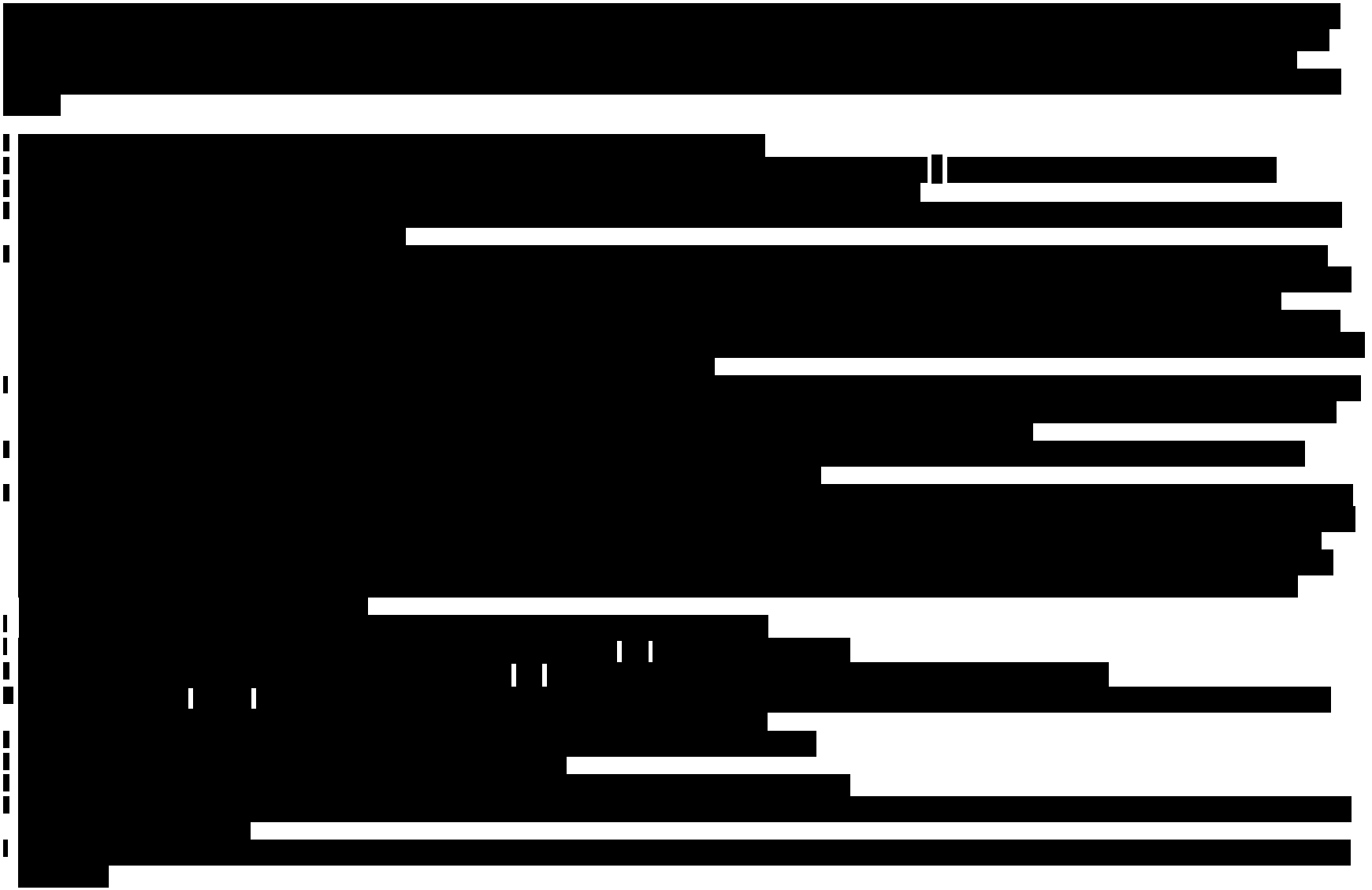
Table 5: Table of Events – Arm C – CC-122 Plus Obinutuzumab (Continued)

	Screening ≤ 28 Days Prior to Day 1[a]	Cycle 1[b, p]							Cycle 2[b]		Cycle 3[b, q]		≥ Cycle 4[b, r]	End of Treatment[b]	Follow-up
	Screen	Day 1	Day 2	Day 4	Day 8 ± 1 Day	Day 9 ± 1 Day	Days 10 and 12 ± 1 Day	Days 16 and 23 ± 1 Day	Day 1	Days 8, 15 and 22 ± 1 Day	Day 1	Days 8, 15 and 22 ± 1 Day	Day 1		28 days post IP discontin-uation
CC-122 Contraceptive and Risk Counseling and Education	To be completed prior to each dispensing of IP as per PPRMP														
HBsAg, anti-HBc, & HCV RNA	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Direct Antiglobulin Test	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Amylase, lipase, fasting lipid profile (eg, cholesterol and triglycerides), creatine kinase, TSH, FT4, LDH, immunoglobulins and T-cell subsets (CD4+, CD8+ and NK cells)	X	X	-	-	-	-	-	-	X	-	X	-	X	X	-
Troponin-T and BNP	X	X	-	-	X	-	-	X	X	-	X	-	X	X	-
12-lead ECG	X	X	-	-	-	X	-	X	X	-	X	-	X	X	-
Ophthalmology Exam[c]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cardiac ECHO or MUGA[d]	X	-	-	-	-	-	-	-	X	-	-	-	X[d]	X	-
[redacted]	X	-	-	-	-	-	-	-	-	-	-	-	X[e]	X[e]	-
Efficacy Response Assessment [f]	-	-	-	-	-	-	-	-	-	-	-	-	X[f]	X	-
[redacted]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 5: Table of Events – Arm C – CC-122 Plus Obinutuzumab (Continued)

	Screening ≤ 28 Days Prior to Day 1[a]	Cycle 1[b, p]							Cycle 2[b]		Cycle 3[b, q]		≥ Cycle 4[b, r]	End of Treatment[b]	Follow-up
	Screen	Day 1	Day 2	Day 4	Day 8 ± 1 Day	Day 9 ± 1 Day	Days 10 and 12 ± 1 Day	Days 16 and 23 ± 1 Day	Day 1	Days 8, 15 and 22 ± 1 Day	Day 1	Days 8, 15 and 22 ± 1 Day	Day 1		28 days post IP discontin-uation
Bone Marrow Aspirate/ Biopsy[g]	X	-	-	-	-	-	-	-	-	-	-	-	X[g]	-	-
Peripheral Blood for MRD Assessment[h]	X	-	-	-	-	-	-	-	-	-	-	-	X[h]	-	-
[redacted]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[redacted]	X	-	-	-	-	-	-	-	-	-	-	-	-	X	-
[redacted]	X	-	-	-	-	X[j]	-	-	X[j]	X[j]	-	X[j]	X[j]	-	-
[redacted]	-	-	-	-	-	X	-	X[k]	-	X[k]	-	X[k]	-	-	-
Administer Obinutuzumab[m]	-	X	X	-	X	-	-	X	X	-	X	-	X	-	-
Dispense CC-122	-	-	-	-	-	X	-	-	X	-	X	-	X	-	-
Drug Accountability/Compliance	-	-	-	-	-	-	-	-	X	-	X	-	X	X	-
[redacted]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]	-	X	X	X	X	X	X	X	X	X	X	X	X	X	-
[redacted]	X	X	X	X	X	X	X	X	-	-	-	-	-	-	-
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[redacted]



Please refer to Section 6 for a detailed description of Arm C procedures.

6. PROCEDURES

As of 05 Jul 2018, enrollment of new subjects into Phase 1 has been discontinued, and Phase 2 will not proceed. Subjects already enrolled who are receiving clinical benefit in the opinion of the treating investigator may continue to receive study treatment up to a maximum of 24 cycles of CC-122.

The screening period begins on the date the Informed Consent Document (ICD) is signed and will last for up to 28 days. The ICD must be obtained prior to beginning any assessments solely for the purpose of this study. Standard of care assessments performed prior to signing the ICD (as described in the protocol) may be used for this study, assuming they meet the protocol requirements and following discussion with the sponsor's medical monitor. Recording of AEs/serious adverse events (SAEs) will begin once the subject has signed the ICD. All prior anticancer treatments (eg, chemotherapy, surgeries) and medical history, including approximate dates of treatment or diagnosis, must be recorded during screening.

All study-required procedures should be performed as outlined in Table 3 through Table 5, depending on the arm to which the subject is assigned:

Table	Arm
Table 3	Arm A: CC-122 single agent with intrasubject dose escalation
Table 4	Arm B: CC-122 in combination with ibrutinib
Table 5	Arm C: CC-122 in combination with obinutuzumab

As of Protocol Amendment 7, some clinic visits and assessments may be omitted as noted in Table 3 through Table 5, and in Section 6.6 below.

Excursions from the timing of assessments will be considered protocol deviations and should be recorded in the source document along with the reason for the excursion.

All scheduled laboratory assessments are to be performed at the designated central laboratory. However, local laboratories may be used for the biweekly assessments (Days 8 and 22) during the third cycle of CC-122 dosing, and for decisions affecting treatment and dose modifications. For subjects on Arm A who dose escalate every 2 weeks, local laboratories may be used however the designated central laboratory is recommended.

All laboratory values should be carefully monitored, especially following the initial treatment, throughout the first two cycles and for dose escalations of CC-122. Serum creatinine and creatinine clearance, uric acid, phosphorus, calcium, and potassium labs should be monitored closely on Days 1, 2, 4, and 8 during the first cycle of CC-122 (ie, Cycle 1 in Arms A and C) and (Cycle 2 in Arm B) [redacted] and unscheduled assessments performed as needed.

6.1. Safety Assessments

Study safety evaluations will occur in accordance with Table 3 through Table 5, and should be performed in accordance with this section of the protocol. The safety of CC-122 single agent

and CC-122 in combination with ibrutinib and in combination with obinutuzumab will be assessed using AEs, physical examinations (PEs), concomitant medications and procedures, clinical laboratory tests, vital signs, electrocardiograms (ECGs), and an echocardiogram/multi-gated acquisition scan (MUGA).

Detailed procedures for obtaining each assessment are provided below.

6.1.1. Demographics / Medical History / Baseline Stage and Prognostic Classification

Demographics (gender, race, ethnicity, and date of birth), medical history, and the Cumulative Illness Rating Scale (CIRS) Score (Appendix G) will be documented by a qualified clinician at the time of the Screening visit. The medical history will be general enough to document common comorbid conditions as well as specific enough to reveal any conditions listed as participation exclusion criteria, and will document whether the identified conditions are active or inactive at the time of enrollment. The CIRS score will be collected to assess the performance status and fitness of subjects. [redacted]

6.1.1.1. Prognostic Classification

Chronic lymphocytic leukemia-specific international prognostic classification reflecting the subject's status at the time of enrollment will be documented [redacted]

6.1.2. Adverse Events

All subjects will be evaluated for AEs during all scheduled visits starting at the signing of the ICD until 28 days after the last dose of study treatment.

6.1.3. Vital Signs

Vital sign measurements will be obtained at each visit as indicated in Table 3 through Table 5. These assessments include systolic and diastolic blood pressure, heart rate, respiration rate, body temperature and body weight. Measurements of height will be recorded only at the Screening visit.

Vital signs should be measured after the subject has rested for at least 5 minutes. Vital sign measurements should be repeated for confirmation if clinically significant observations or changes from baseline occur. All confirmed, clinically significant vital sign measurements must be recorded as an AE.

After the first 12 cycles of CC-122, in the absence of Grade ≥ 2 adverse events related to CC-122, and as clinically indicated, some clinic visits and assessments may become less frequent as detailed in Section 6.6.

6.1.4. Physical Examination

Complete PEs, including evaluation of lymph nodes, spleen and liver will be performed during Screening, on Cycle 1 Day 1 and will continue to be performed on Day 1 of each subsequent treatment cycle under Protocol Amendment 7 as part of the assessment for response (in the absence of imaging), at the EOT visit and at 28 days after the last IP discontinuation. Measurements of lymph nodes and documentation of any enlargement of the spleen and/or liver should be recorded in the source document and eCRF.

Symptom driven limited PEs will be performed as clinically indicated at any study visit.

6.1.5. Cardiac Laboratory Testing

Subjects will undergo laboratory monitoring of plasma troponin-T and B-type natriuretic peptide (BNP) to evaluate for potential early evidence of cardiac toxicity. Testing will be performed at Screening, weekly during the first cycle of CC-122 treatment and for the first cycle of each dose escalation (Days 1, 8, 15, and 22), Day 1 of each subsequent cycle, and at the EOT visit. A significant elevation of troponin-T is defined as a value greater than the upper limit of normal (ULN) for the assay with associated elevation of BNP or other significant cardiac symptoms or findings. A significant elevation of BNP is defined as a ≥ 20% increase over baseline with an absolute value > 100 pg/mL. Subjects who are found at Screening to have baseline troponin-T > ULN or BNP > 100 pg/mL must have a baseline evaluation by a cardiologist during screening to optimize cardioprotective therapy.

After the first 12 cycles of CC-122, in the absence of Grade ≥ 2 adverse events related to CC-122, and as clinically indicated, some clinic visits and assessments may become less frequent as detailed in Section 6.6.

6.1.6. 12-Lead Electrocardiogram

Triplicate or single standard 12-lead ECGs will be recorded at the visits listed in Table 3 through Table 5. The 12-lead ECGs (12-lead at 25 mm/sec reporting rhythm, ventricular rate, PR-interval, QRS complex, QT interval, and QTc interval) will be performed after the subject has been in the supine position for at least 5 minutes.

Triplicate ECGs (3 recordings within 2±1 minute intervals) will be performed at Screening for all subjects. In addition, triplicate ECGs will be collected as follows:

Arm A: Cycle 1 Day 1: 0 and 1.5 hours (±15 minutes) after CC-122 dosing

Arm B: Cycle 1 Day 1: 0 and 1.5 hours (±15 minutes) after ibrutinib dosing

Cycle 2 Day 1: 0 and 1.5 hours (±15 minutes) after CC-122 dosing

Cycle 2 Day 15: 0 and 1.5 hours (±15 minutes) after CC-122 dosing

Arm C: Cycle 1 Day 1: 0 and 1.5 hours (±15 minutes) after obinutuzumab dosing

Cycle 1 Day 9 and Cycle 1 Day 23: 0 and 1.5 hours (±15 minutes) after CC-122 dosing

A single ECG will be performed on all other visits where an ECG is indicated per Table 3 through Table 5 approximately 1.5 hours (±15 minutes) after dosing.

After the first 12 cycles of CC-122, in the absence of Grade ≥ 2 adverse events related to CC-122, and as clinically indicated, some clinic visits and assessments may become less frequent as detailed in Section 6.6.

6.1.7. Left Ventricular Ejection Fraction

Left ventricular ejection fraction (LVEF) MUGA, or echocardiogram (ECHO) will be conducted at Screening, after the first cycle of CC-122, and every 3 cycles thereafter (± 7 days), and at the EOT if not performed within the previous 8 weeks.

After the first 12 cycles of CC-122, in the absence of Grade ≥ 2 adverse events related to CC-122, and as clinically indicated, some clinic visits and assessments may become less frequent as detailed in Section 6.6.

6.1.8. Clinical Laboratory Tests

The following laboratory assessments will be performed at the Screening visit and during the study at the time points as described in Table 3 through Table 5. All samples will be analyzed at a central laboratory unless otherwise specified. All samples should be drawn predose unless otherwise specified. Laboratory assessments will be recorded in the source document and eCRF:

- Amylase, lipase, fasting lipid profile, creatine kinase, thyroid-stimulating hormone (TSH), free T4 (FT4), immunoglobulins (IgG, IgM and IgA only), T-cell subsets
- CBC: hemoglobin, hematocrit, red blood cell count with indices, white blood cell count with absolute differential and platelet count.
- Serum chemistry: albumin, total protein, bicarbonate, calcium, phosphorus, serum creatinine, serum urea/blood urea nitrogen (BUN), glucose (fasting), potassium, sodium, magnesium, chloride, total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST or serum glutamic oxaloacetic transaminase [SGOT]), alanine aminotransferase (ALT or serum glutamate pyruvic transaminase [SGPT]), and lactate dehydrogenase (LDH) and uric acid.
- Beta-2 Microglobulin

- C-reactive protein
- Direct antiglobulin test (local laboratory only)
- Coagulation tests: prothrombin time, international normalized ratio, and partial thromboplastin time
- Urinalysis: dipstick, with microscopy in event of positive (1+ or greater) blood or protein and 24-hour collection for creatinine clearance and protein quantification in the event of 2+ or greater protein.
- Virus Serology: hepatitis B antigen (HBsAg), hepatitis B core antibody (anti-HBc), and hepatitis C virus (HCV) RNA

After the first 12 cycles of CC-122, in the absence of Grade ≥ 2 adverse events related to CC-122, and as clinically indicated, some clinic visits and assessments may become less frequent as detailed in Section 6.6.

6.1.9. Prior/Concomitant Medications and Procedures

All subjects will be evaluated for any concomitant medications and procedures during all scheduled visits from the signing of the ICD until 28 days after the last dose of study treatment.

[redacted]

6.1.12. Ophthalmologic Examinations

An ophthalmologic examination will be performed by a qualified ophthalmologist at Screening as described below in all subjects. The Screening ophthalmologic exam will include:

- Visual acuity
- Slit-lamp examination with fluorescein staining following pupillary dilation (unless fluorescein and pupillary dilatation are contraindicated)

- Ophthalmologic examination focusing on the anterior chamber, iris and anterior vitreous

Subsequent ophthalmologic examinations will be performed as clinically indicated. If there are any clinically significant findings, a full ophthalmologic exam will be conducted by a qualified ophthalmologist.

6.1.13. Contraceptive and Risk Counseling

Subjects will be counseled about appropriate contraception during Screening. Complete abstinence or double contraceptive methods (one of which must be a barrier method) for females (eg, oral, injectable, or implantable hormonal contraceptive; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner) must be used from the time ICF is signed, throughout the study and for 28 days after the last dose of CC-122. A single contraceptive method for males (complete abstinence or a condom) must be used from the time the ICF is signed, throughout the study, and for 3 months after the last dose of CC-122. Counseling should be documented in source documents.

The CC-122 Pregnancy Risk Minimization Plan for Celgene Clinical Trials (Appendix F) applies to all subjects receiving CC-122 therapy and will be given to sites as a separate document.

CC-122 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, or designee, in requirements specific to counseling of subjects.

Once trained, these healthcare staff will counsel subjects prior to the administration of CC-122 to ensure that the subject has complied with all requirements including use of birth control and that the subject understands the risks associated with CC-122. This step will be documented with a completed Education and Counseling Guidance Document, and CC-122 will not be administered until this step occurs.

A CC-122 Information Sheet will be provided to each subject before IP is dispensed.

Females of childbearing potential and males, other than the subject, should not handle or administer CC-122 unless they are wearing gloves.

Arm C: Females of childbearing potential should use effective contraception during obinutuzumab treatment and for 18 months following obinutuzumab therapy (GAZYVA, GAZYVARO).

Arm B: Females of childbearing potential should avoid becoming pregnant while taking ibrutinib because ibrutinib can cause fetal harm (IMBRUVICA).

6.1.14. Pregnancy Test

A female of child bearing potential (FCBP) is defined as a sexually mature woman who has:

1. Not undergone a hysterectomy or bilateral oophorectomy, and
2. Not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

The investigator will classify a female subject as a FCBP according to this definition. Pregnancy testing is not required for non-FCBP subjects but justification must be recorded in the eCRF and the source document. Pregnancy testing will be conducted by the local laboratory.

For a FCBP, pregnancy testing will be conducted at the visits listed in Table 3 through Table 5:

- A serum pregnancy test with sensitivity of at least 25 mIU/mL is to be obtained at Screening.
- A serum or urine pregnancy test (based on investigator's discretion and minimum test sensitivity [25 mIU/mL]) should be done weekly for the first cycle, within 72 hours prior to Day 1 of every cycle (with the exception of the first day of CC-122 dosing on which it must be performed within 24 hours of first dose), EOT visit and 28 days post IP discontinuation.
- The subject may not receive IP until the investigator has verified the Screening pregnancy tests to be negative.
- A FCBP must avoid activities that could lead to conception for 28 days after the last dose of CC-122 or a male subject whose partner is an FCBP must avoid activities that could lead to conception for 3 months after the last dose of CC-122.
- Please refer to the ibrutinib and the obinutuzumab PI(s) or SmPC(s) for additional recommendations.

Note: FCBP receiving CC-122 will undergo pregnancy testing according to the schedule described in the CC-122 Pregnancy Prevention Risk Management Plan (PPRMP) and CC-122 Information Sheet.

Results for pregnancy tests will be recorded in the source document and eCRF.

6.2. Efficacy Assessments

6.2.1. Efficacy Parameters

The following efficacy assessments will be performed at scheduled intervals throughout the study as described in Table 3 through Table 5.

6.2.2. Tumor Imaging Assessment

Tumor imaging assessment by CT scan is mandatory at Screening (neck, chest, abdomen, and pelvis), and after the first 6 cycles of CC-122 dosing [the 2nd scan is mandatory only for the affected regions with abnormal findings at baseline; Week 25 (for subjects on Arms A and C) or Week 29 (for subjects on Arm B), +4 weeks/-1 week], and is recommended if the subject discontinues study treatment due to an adverse event (if the subject shows signs of preliminary efficacy). Additional CT scan(s) is allowed if clinically indicated until documented disease progression or initiation of subsequent CLL therapy. The unscheduled CT scan(s) should be documented in the CRF. A CT scan with contrast is the recommended imaging modality. MRI may be used only if CT with contrast is medically contraindicated or if the frequency of CT scans exceeds local standards. Standard of care CT scans or MRI performed up to 56 days prior to Cycle 1 Day 1 may be acceptable for Screening, even if performed prior to signing the ICD. All imaging assessments will be evaluated by a reader at the local institution.

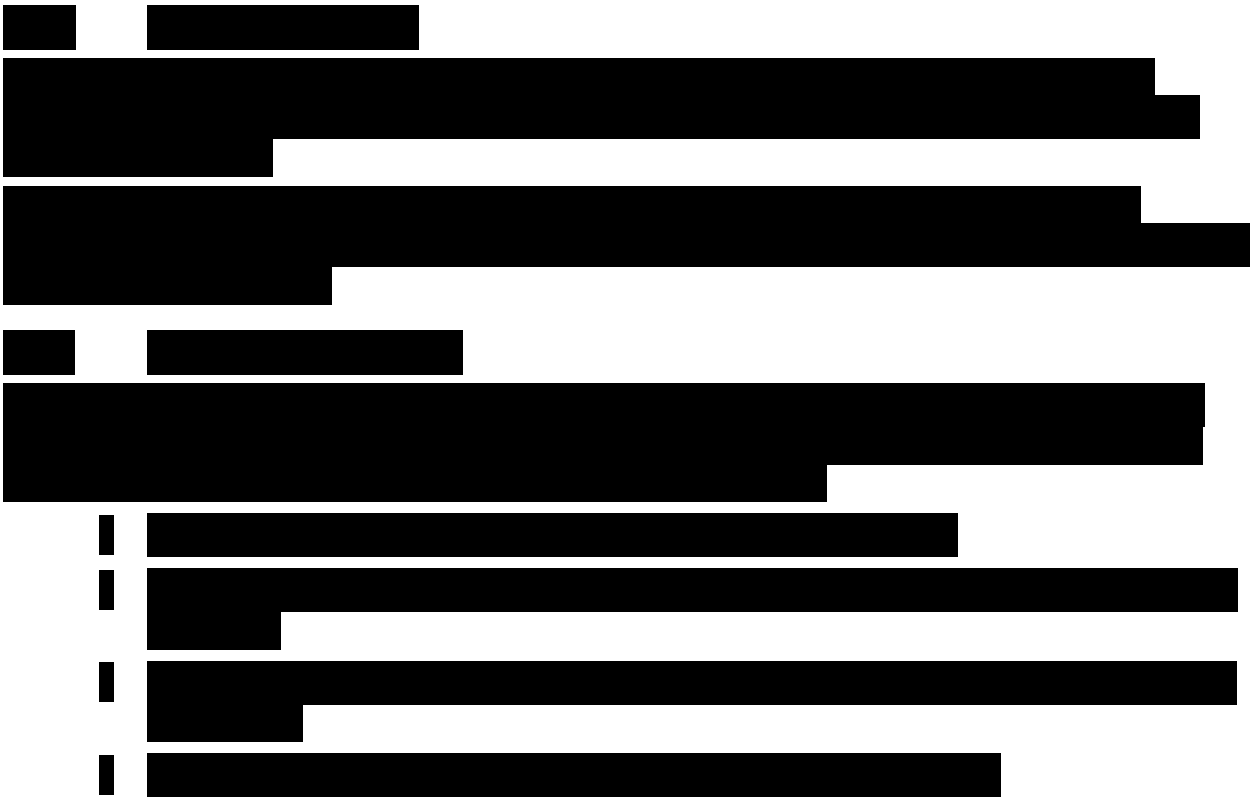
6.2.3. Bone Marrow Examination

A bone marrow aspirate and biopsy are optional for all subjects at Screening. A bone marrow aspirate and biopsy must be collected for all subjects at the time of the CR/CRi confirmation visit within 12 weeks after clinical, imaging, and laboratory response criteria have been met.

6.2.4. Minimal Residual Disease (MRD) Assessment

Peripheral blood for MRD assessment should be collected during Screening, every 6 cycles (only if subject is receiving CC-122, up to a maximum of 24 cycles), and at the time of CR/CRi confirmation visit (within 12 weeks after clinical and laboratory response criteria have been met). For those subjects found to be MRD positive in the peripheral blood at the CR/CRi confirmation visit, a peripheral blood sample for MRD assessment should be collected approximately every 6 cycles thereafter until MRD negativity is achieved or relapse/progression is documented. Peripheral blood for MRD assessment should also be collected at the time of PR (within 12 weeks after clinical, imaging, and laboratory response criteria have been met). A bone marrow aspirate for MRD assessment should be collected at the time of CR/CRi confirmation visit and once MRD-negativity is achieved in peripheral blood unless MRD negativity in bone marrow was documented earlier. Peripheral blood for MRD assessment should also be collected at the time of relapse/progression in subjects who previously achieved MRD negativity in peripheral blood.

MRD analyses will be performed by a central laboratory.



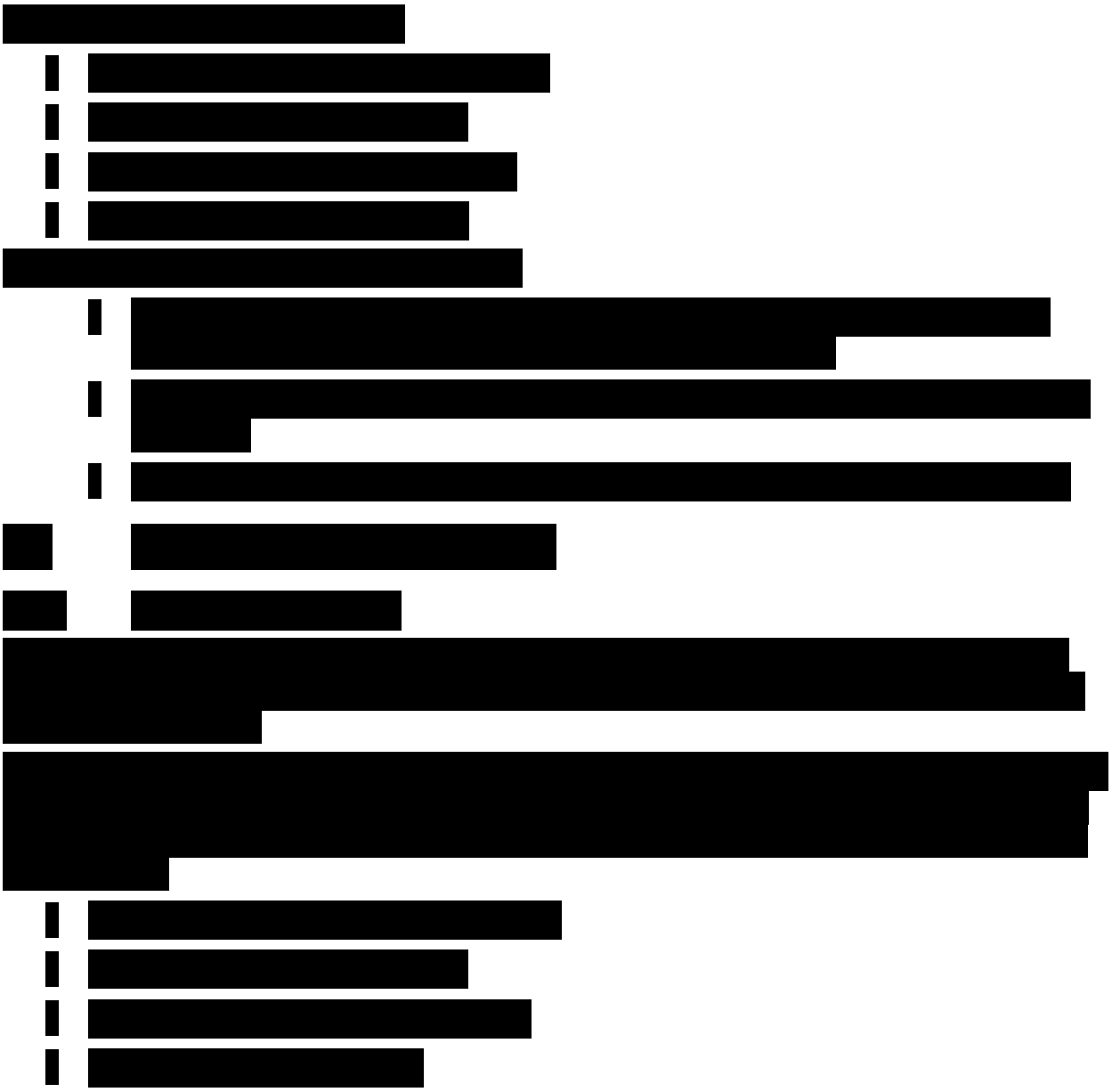
[redacted]

6.2.7. Efficacy Response Assessment

Response assessment for CLL will be completed according to the updated IWCLL guidelines for the diagnosis and treatment of CLL as described in Appendix A with modifications. Subjects with SLL will be assessed according to the lymphoma guidelines as described in Appendix B. Lymph node responses will be assessed separately and independently of increases in blood lymphocyte counts.

Efficacy response according to the respective criteria for CLL/SLL will be formally assessed at the same schedule as CT scans and at the End of Treatment visit. In addition, efficacy assessment should also be performed every 3 cycles (+4 weeks/-1 week) during the first two years and every 6 cycles (+4 weeks/-1 week) thereafter at the time of physical examinations until documented progression or initiation of subsequent CLL therapy. CR/CRi confirmation by bone marrow examination must be completed within 12 weeks after clinical criteria have been met.

[redacted]



[redacted]

6.5. Phase 1 Dose Escalation - Third Cycle of CC-122 Through the Twelfth Cycle of CC-122

During the third cycle of CC-122, the Day 8 and/or Day 22 clinic visits and assessments may be omitted at the discretion of the investigator in the absence of any Grade ≥ 2 toxicity related to CC-122.

Thereafter, the minimum frequency of visits is once monthly (until the first 12 cycles of CC-122 have been completed, see Section 6.6) and appropriate procedures/tests are expected to be performed. Note that the drug dispensed at a given visit should cover the anticipated time to the next scheduled visit. Owing to the requirements of the PPRMP and its proscriptions concerning the availability of drug and the importance of pregnancy testing and counseling, a subject must visit with a minimum frequency of every 28 days.

6.6. Phase 1 Dose Escalation - Cycle 13 of CC-122 and Beyond

Beginning with Cycle 13 of CC-122, the following Day 1 clinic visits and assessments may be performed on a less frequent schedule at the discretion of the investigator in the absence of any Grade ≥ 2 toxicity related to CC-122.

- **Tests to occur every cycle (can be up to 7 days prior to Day 1) in order for CC-122 to be dispensed:**
  - Serum or urine pregnancy test in females of childbearing potential as per CC-122 PPRMP (Appendix F, Section 19).
  - CC-122 Contraceptive and Risk Counseling and Education (Appendix F, Section 19).
  - Hematology: CBC with differential and platelet counts.
  - Laboratory test may be performed up to 48 hours before the visit.
  - Physical Examination.
  - Recording of adverse events:
    - Subjects will be queried on any new adverse events that were experienced by the subject and recorded in the source documents and CRFs.
  - Recording of concomitant medications and procedures
- **Tests to occur every 1-3 months (± 7 days) in the absence of any Grade ≥ 2 toxicity related to CC-122:**
  - Vital signs and weight
  - [redacted]
  - Laboratory tests (may be performed up to 48 hours before the visit):
    - Serum chemistries: albumin, total protein, bicarbonate, calcium, phosphorus, serum creatinine, serum urea/BUN, glucose (fasting), potassium, sodium, magnesium, chloride, total bilirubin, alkaline phosphatase, AST, ALT, LDH, and uric acid
    - C-Reactive Protein
    - Cardiac-specific troponin-T, BNP
    - PT/INR/PTT
    - Amylase, lipase, fasting lipid profile, creatine kinase, TSH, FT4, immunoglobulins
    - Urinalysis with microscopy
  - [redacted]
  - 12-lead single ECG (3 recordings within 2 ± 2 minute intervals) will be performed both at predose (within 90 minutes prior to dosing) and at 1.5 hours post dose
  - LVEF by ECHO or MUGA only if clinically indicated
  - T-cell subsets should continue to be obtained on Day 1 of each cycle

7. STUDY POPULATION

7.1. Number of Subjects and Sites

The study population consists of Dose Escalation Phase (Phase 1) subjects who were enrolled under previous amendments and were ongoing during Amendment 6, version dated 06 Jun 2017. As of 05 Jul 2018, enrollment of new subjects into Phase 1 has been discontinued and Phase 2 will not proceed.

Depending on the tolerability of each dose level, this study will enroll approximately 158 (136-182) subjects. The Dose Escalation Phase will include the following:

- Arm A: 20 subjects
- Arm B: 24 (18 to 36) subjects
- Arm C: 24 (18 to 36) subjects

The Dose Expansion Phase may enroll up to 50 subjects in Arm B and/or 40 subjects in Arm C for a total of up to 90 subjects.

Subjects will be enrolled in the US, Canada and Europe.

7.2. Inclusion Criteria

As of 05 Jul 2018, enrollment of new subjects into Phase 1 has been discontinued and Phase 2 will not proceed.

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

1. Subjects ≥ 18 years age and ≤ 80 years of age at the time of signing the informed consent form.
2. Understand and voluntarily sign an informed consent form prior to any study related assessments/procedures being conducted.
3. Able to adhere to the study visit schedule and other protocol requirements.
4. Must have a documented diagnosis of CLL/SLL requiring treatment (IWCLL Guidelines for the Diagnosis and Treatment of CLL [Hallek, 2008]). In addition:
    a. Presence of at least one clinically measurable lesion:
        i. nodal lesion that measures ≥ 1.5 cm in longest dimension (LD) and ≥ 1.0 cm in longest perpendicular dimension (LPD), or
        ii. spleen that measures ≥ 14 cm in longest vertical dimension (LVD) with a minimum of 2 cm enlargement, or
        iii. liver that measures ≥ 20 cm in LVD with a minimum of 2 cm enlargement, or
        iv. peripheral blood B lymphocyte count > 5000/uL

5. Must meet the criteria for relapsed and/or refractory disease according to the IWCLL guidelines [redacted] to ≥ 1 prior treatment (with the exception of Arm B) and have evidence of disease progression requiring treatment at the time of study entry as follows:
    a. For Arms A and C, subjects must have received either prior chemoimmunotherapy or therapy with an approved BTK inhibitor with the following exceptions:
        i. Chemoimmunotherapy is not required if subjects have specific co-morbidities that preclude the use of standard chemoimmunotherapy meeting at least 1 of the following criteria;
            1. CIRS ≥ 6;
            2. Creatinine Clearance < 70 mL/min;
            3. Subject is not a candidate for a chemoimmunotherapy in the opinion of investigator.

        The reason for not being a candidate must be documented in the CRF.
        ii. Treatment with an approved BTK inhibitor is not required if subject has contraindications or is not a candidate for such a therapy in the opinion of the investigator.

        The reason for not being a candidate must be documented in the CRF.
    b. For Arm B, subjects with treatment-naïve or R/R CLL must meet the following criteria:
        i. Dose Escalation Phase: Subjects must not have received prior treatment with ibrutinib (or any other BTK inhibitors) and must have:
            1. R/R CLL: has 17p- and/or TP53 mutation; or
            2. Treatment naïve: is unfit for standard chemoimmunotherapy meeting at least 1 of the following co-morbidity criteria:
                a. CIRS ≥ 6;
                b. Creatinine Clearance < 70 mL/min;
                c. Subject is not a candidate for a chemoimmunotherapy in the opinion of the investigator.

        The reason for not being a candidate must be documented in CRF.
        ii. Dose Expansion Phase: Subjects must not have received prior treatment with ibrutinib (or any other BTK inhibitors) and must have high risk CLL. High risk is defined as:
            1) 17p- and/or TP53 mutation positive in treatment naïve CLL; or
            2) 17p- and/or TP53 mutation positive, and/or complex karyotype, and/or progression < 24 months after completion of 1st line chemoimmunotherapy in R/R CLL

c. Subjects with R/R SLL or CLL with bulky disease (at least one lymph node measuring > 5.0 cm in diameter) are considered at higher risk for developing TFR and may only be enrolled upon discussion with the sponsor's medical monitor and agreement to close medical management.

6. Subjects must have the following lab values:
   a. Absolute neutrophil count (ANC) ≥ 1,500 cells/mm^3 or ≥ 1000 cells/mm^3 if secondary to bone marrow involvement by disease.
   b. Platelet count ≥ 100,000 cells/mm^3 (100 x 10^9/L) or ≥ 50,000 cells/mm^3 (50 x 10^9/L) if secondary to bone marrow involvement by disease.
   c. Serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) < 3.0 x upper limit of normal (ULN) unless due to disease.
   d. Serum bilirubin < 1.5 x ULN unless due to Gilbert's syndrome.
      - Serum bilirubin ≤ 1.0 x ULN unless due to Gilbert's syndrome, **Treatment Arm B only (CC-122 in combination with ibrutinib)**
   e. Calculated creatinine clearance of ≥ 60 ml/min.
   f. No evidence of TLS per the Cairo-Bishop definition of laboratory TLS (Appendix E) (subjects may be enrolled upon correction of electrolyte abnormalities).

[redacted]

8. Ability to swallow oral capsules without difficulty.
9. Pregnancy Prevention Risk Management Plan:
   a. Females of childbearing potential (FCBP) must undergo pregnancy testing based on the frequency outlined in the PPRMP and pregnancy results must be negative.
   b. Unless practicing complete abstinence from heterosexual intercourse, sexually active FCBP must agree to use adequate contraceptive methods as specified in the PPRMP.
      - For Arm C, subjects must agree to use adequate contraceptive methods for 18 months (please refer to the obinutuzumab IB, PI, and SmPC).
      - Complete abstinence is only acceptable in cases where this is the preferred and usual lifestyle of the subject.
      - Periodic abstinence (calendar ovulation, symptothermal, post-ovulation methods) and withdrawal **are not acceptable**.
   c. Males (including those who have had a vasectomy) must practice complete abstinence or use barrier contraception (condoms) when engaging in sexual activity with FCBP as specified in the PPRMP.
   d. Males must agree not to donate semen or sperm for the duration of the study and for 3 months after the last dose of CC-122.
   e. All subjects must:
      - Understand that the IP could have a potential teratogenic risk.

- Agree to abstain from donating blood while taking IP and following discontinuation of IP.
- Agree not to share IP with another person.

f. Other than the subject, FCBP and males should not handle the IP or touch the capsules, unless gloves are worn.

g. Be counseled about pregnancy precautions and risks of fetal exposure (see Section 6.1.13).

Arm B only:

10. Enrollment into Arm B will be permitted if ibrutinib is considered the standard of care in the clinical practice.

Expansion Cohort 2 of Arm C:

11. Subjects in Cohort 2 of Arm C must meet the following criteria:

    a. Subject must have received at least one BCR PI (ibrutinib, idelalisib, or other approved BTK or PI3K inhibitor) and/or venetoclax;

    b. Subject must be either resistant to or intolerant of (ie., treatment failures) the last BCR PI and/or venetoclax. Resistant is defined as relapsed or refractory per IWCLL2008:

        i. Relapse is defined as a patient who has previously achieved a CR or PR, but after a period of 6 or more months, demonstrates evidence of disease progression.

        ii. Refractory is defined as failing to achieve a CR or PR, or disease progression within 6 months after initiation of treatment with an approved BTK or PI3K inhibitor (eg, ibrutinib, idelalisib) or venetoclax.

        iii. Intolerance is defined as the inability to continue treatment with a BCR PI or venetoclax due to toxicities or due to development of a contraindication that makes the subject ineligible to receive further treatment with a BCR PI or venetoclax.

7.3. Exclusion Criteria

As of 05 Jul 2018, enrollment of new subjects into Phase 1 has been discontinued and Phase 2 will not proceed.

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

1. Any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
2. Any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study.
3. Any condition that confounds the ability to interpret data from the study.

4. Prior autologous or allogeneic stem cell transplant (SCT)/bone marrow transplant within 12 months of signing the ICD. Subjects who received allogeneic SCT ≥ 12 months before signing the ICD may be eligible provided there is no ongoing graft-versus-host disease and no ongoing immune suppression therapy.
5. Uncontrolled intercurrent illness including, but not limited to:
    a. Ongoing or active infection requiring parenteral antibiotics.
    b. Uncontrolled diabetes mellitus.
        i. The glycemic targets for subjects with diabetes should take into consideration age, comorbidities, life expectancy, and functional status of the subjects and follow established guidelines (eg, International Diabetes Federation, the European Diabetes Working Party guidelines, and the American Diabetes Association). For younger (< 70 years old) or subjects with life expectancy ≥ 10 years, the target glycosylated hemoglobin, type A1C (HbA_{1c}) should be < 7.0%. The target HbA_{1c} for older (≥ 70 years old) subjects or subjects with life expectancy < 10 years should be < 8.0%. Consultation with an endocrinologist is recommended when deciding if diabetes is optimally controlled. Subjects with a stable HbA_{1c} greater than the suggested target may be enrolled upon discussion with the medical monitor.
    c. Chronic symptomatic congestive heart failure (Class III or IV of the New York Heart Association Classification for Heart Disease).
    d. Active central nervous system involvement as documented by spinal fluid cytology or imaging.
    e. Uncontrolled autoimmune hemolytic anemia or thrombocytopenia.
    f. Other concurrent severe and/or uncontrolled concomitant medical conditions that could cause unacceptable safety risks or compromise compliance with protocol.
6. History of second malignancies with life expectancy of < 2 years or requirement of therapy that would confound study results. This does not include the following:
    a. Basal cell carcinoma of the skin.
    b. Squamous cell carcinoma of the skin.
    c. Carcinoma in situ of the cervix.
    d. Carcinoma in situ of the breast.
    e. Carcinoma in situ of the bladder.
    f. Incidental histologic finding of prostate cancer (TNM stage of T1a or T1b).
7. Known seropositivity for or history of active viral infection with human immunodeficiency virus (HIV), or hepatitis B or C virus (HBV, HCV).
    a. Hepatitis B screening is mandatory for all patients (HBsAg and anti-HBc). Patients with active hepatitis B disease should not be treated with obinutuzumab. Patients should be referred to a specialist if they are carriers before treatment

starts (see PI or SmPC). Subjects who are positive for anti-HBc and/or anti-HBs but negative for HBsAg and HBV DNA may be treated after consultation with a hepatologist.

8. Any peripheral neuropathy ≥ NCI CTCAE Grade 2.
9. Use of systemic corticosteroids in doses greater than prednisone equivalent to 20 mg/day.
10. Medicines with high probability to cause QT prolongation or torsades de pointes. Subjects on chronic medications in this category may enroll after discussion with the medical monitor if changing these medications are not in the best medical interest of the patient.
11. History of hypersensitivity to IMiDs® (lenalidomide, pomalidomide, thalidomide).
12. Impaired cardiac function or clinically significant cardiac diseases, including any of the following:
    a. LVEF < 45% as determined by MUGA scan or ECHO.
    b. Complete left bundle branch, or bifasicular, block.
    c. Congenital long QT syndrome.
    d. Persistent or uncontrolled ventricular arrhythmias or atrial fibrillation.
    e. QTcF > 470 msec on Screening ECG (mean of triplicate recordings).
    f. Unstable angina pectoris or myocardial infarction ≤ 6 months prior to starting CC-122.
    g. Uncontrolled congestive heart failure or uncontrolled hypertension.
    h. Troponin-T value >0.4 ng/mL or BNP >300 pg/mL.

       Subjects with baseline troponin-T >ULN or BNP >100 pg/mL are eligible but should have cardiologist evaluation prior to enrollment in the trial for baseline assessment and optimization of cardioprotective therapy and after discussion with the sponsor's medical monitor.
13. Chemotherapy, radiotherapy, investigational anticancer therapy or major surgery within 28 days of Day 1 dosing with the following exceptions:
    a. Arm A: A minimum 5-day washout after discontinuation of ibrutinib (or other BTK inhibitors) is required; only those subjects without rapid disease progression during the 5-day washout will be allowed to enroll into Arm A.
       i. Rapid disease progression is defined as follows:
          1. For subjects with measurable nodal disease, the increase in the sum of diameters of the largest lymph nodes (up to 3 nodes) exceeds 1 cm per day OR the diameter of the largest lymph node exceeds 5 cm during the 5 day wash out.
          2. For subjects with lymphocytosis, the increase in the ALC exceeds $2x10^9$/L per day OR the ALC exceeds 100,000 $x10^9$/L during the 5-day wash out;

b. Arm C: No minimum washout is required after discontinuation of ibrutinib (or other BTK inhibitors)

c. Approved PI3 kinase inhibitors: Subjects may start study treatment within 3 days of discontinuation of approved PI3 kinase inhibitors.

14. Persistent diarrhea or malabsorption ≥ NCI CTCAE Grade 2, despite medical management.
15. Active disease transformation (ie, Richter's Syndrome); subjects with Richter's Syndrome that has resolved > 2 years from signing the ICD are eligible.
16. Known acute or chronic pancreatitis
17. Pregnant or lactating females

Arm B only (CC-122 in combination with ibrutinib):

18. Prior treatment with a BTK inhibitor
19. Presence of transfusion-dependent thrombocytopenia or a history of bleeding disorders or clinical conditions (eg, gastrointestinal bleeding or constitutional disorders) that may increase risk of life-threatening bleeding when thrombocytopenic
20. History of stroke or intracranial hemorrhage within 6 months prior to signing the ICD
21. Medications that are strong inhibitors or inducers of CYP3A4/5 (eg, itraconazole, ketoconazole, clarithromycin, ritonavir, phenytoin, pentobarbital, and rifampin) should be changed; subjects who cannot change these medications must be excluded (see Appendix H for a list of strong and moderate inhibitors/strong inducers of CYP3A).
22. Use of concomitant anticoagulation with warfarin or other vitamin K antagonists is prohibited, as is treatment with these agents in the 7 days prior to signing the ICD. The use of other anticoagulants (eg, heparins) and anti-platelet agents is allowed per investigator's discretion. Investigator questions regarding this should be addressed to the sponsor's medical monitor or the study national Principal Investigators.

Arm C only (CC-122 in combination with obinutuzumab):

23. Hypersensitivity to obinutuzumab

8. DESCRIPTION OF STUDY TREATMENTS

8.1. Description of Investigational Products

8.1.1. CC-122

Celgene Corporation will supply CC-122 in appropriate strengths. The active pharmaceutical ingredient in capsules (AIC) was employed from the beginning of the current study (non-formulated, white opaque gelatin capsules). There are no other excipients in the capsules.

During the course of the current study, a new formulation, Formulation 6 [F6] of CC-122 is being developed at various strengths (0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, 2.5 mg, 3.0 mg, 3.5 mg, 4.0 mg) to be made available over the course of the study. The F6 formulations have different CC-122 base free amounts compared to the CC-122 AIC that was employed from the beginning of the current study. CC-122 AIC 0.5, 1, and 3 mg strengths were based on CC-122 HCl and are equivalent to 0.44, 0.88, and 2.64 mg CC-122 base free, respectively. CC-122 formulated capsules of 0.5, 1, 1.5, 2, 2.5, 3, 3.5 and 4 mg strengths are based on CC-122 base free and are equivalent to 0.56, 1.13, 1.69, 2.25, 2.81, 3.38 , 3.95 and 4.51 mg CC-122 HCl, respectively.

Study CC-122-CP-002 Part 2 was an open-label, randomized, three-period, six-sequence, three-way single-dose crossover study in healthy adult subjects to evaluate the PK of CC-122 after administration of formulated (test formulations: Formulation 4 [F4] and F6) and AIC CC-122 capsules.

Following a single oral administration of CC-122 at the dose level of 3 mg from reference AIC formulation and formulated capsule F-6 formulation in healthy adult subjects (N=18), the total plasma exposures (AUC_{inf}) is 16.29% higher and the peak plasma exposure (C_{max}) is 35.58% higher from the F-6 formulation as compared to that from the reference AIC formulation. The CC-122 F-6 formulation has been selected for further development (Data on File, 2015).

For subjects on Arm A, subjects who start with AIC will continue to receive AIC; subjects who start with F6 will continue to receive F6 for all dose levels.

For subjects on Arms B and C, F6 will be introduced in the 1.0 mg cohorts after the 0.5 mg AIC fixed-dose cohort has been completed, and will continue to receive F6 thereafter. The 0.5 mg fixed dose cohorts will use AIC. Any subjects requiring doses of 0.25 mg or lower due to dose reductions will use AIC.

The formulated capsules will be provided in reddish brown gelatin capsules and contain the following excipients: Avicel PH 102, spray dried mannitol, crospovidone, areosil, and stearic acid.

Celgene will continue to provide up to 24 cycles of CC-122 for ongoing patients experiencing clinical benefit.

Please refer to the CC-122 IB and pharmacy manual for detailed information concerning the physical properties of CC-122.

The IP will be labeled per local regulations. Store as directed on package label.

8.1.2. Ibrutinib

Ibrutinib will be supplied by Celgene and labeled appropriately as investigational material for the study. Ibrutinib is supplied as 140 mg capsules. The recommended dose of ibrutinib for subjects with CLL according to the ibrutinib package insert or SmPC (IMBRUVICA) is 420 mg (three 140 mg capsules) orally once daily. Refer to Section 8.2.2.2 for administration information.

Celgene will continue to provide an investigational supply of ibrutinib for ongoing patients experiencing clinical benefit, for up to 24 cycles of CC-122. For patients who discontinue CC-122 prior to 24 cycles or if patients have surpassed the 24 cycles of CC-122, Celgene will continue to provide an additional 3 cycles of ibrutinib from the investigational supply to allow time for patients to be switched to commercially available ibrutinib and/or other therapies at the discretion of the treating physician.

Refer to the Pharmacy manual, package insert, or SmPC for stability and storage information.

8.1.3. Obinutuzumab

Obinutuzumab will be supplied by Celgene and labeled appropriately as investigational material for the study.

Refer to the obinutuzumab IB, package insert or SmPC (GAZYVA, GAZYVARO) for preparation and administration information. Refer to Section 8.2.2.3 for timing of obinutuzumab administration. Premedicate according to the PI, SmPC, or institutional standards. Recommended premedications will be provided by the investigational site. The sponsor will not provide these medications.

Obinutuzumab is to be administered only as an intravenous (IV) infusion.

Celgene will continue to provide the protocol-specified total of 6 cycles of investigational supply of obinutuzumab for ongoing patients experiencing clinical benefit. In the event CC-122 is discontinued prior to obinutuzumab, subjects may continue to receive the protocol-specified total of 6 cycles of obinutuzumab at the discretion of the treating physician. In addition, for patients that have surpassed the 24 cycles of CC-122, Celgene will continue to provide an additional 3 cycles of CC-122 to allow time for patients to be switched to commercially available therapies at the discretion of the treating physician.

Refer to the Pharmacy manual, PI, or SmPC for stability and storage information.

8.1.4. Premedications

Other recommended medications such as allopurinol will be provided by the investigative site. The sponsor will not provide these medications.

Please refer to Section 9.3.3 for required premedications for obinutuzumab infusions.

8.2. Treatment Administration and Schedule

As of 05 Jul 2018, enrollment of new subjects into Phase 1 has been discontinued and Phase 2 will not proceed.

CC-122-CLL-001 is a Phase 1/2 open-label, dose finding study evaluating CC-122 administered orally to subjects with CLL/SLL. Subjects who are eligible for the study will be assigned to one of the following arms:

- **Arm A:** CC-122 single agent
- **Arm B:** CC-122 in combination with ibrutinib
- **Arm C:** CC-122 in combination with obinutuzumab

Cycle 1 Day 1 treatment may begin if the following parameters are met:

- All eligibility criteria
- The ANC is $\geq$ 1,500 cells/mm^3 (1.5 x 10^9/L) or $\geq$ 1,000 cells/mm^3 (1.0 x 10^9/L) if secondary to bone marrow involvement by disease
- The platelet count is $\geq$ 100,000 cells/mm^3 (100 x 10^9/L) or $\geq$ 50,000 cells/mm^3 (50 x 10^9/L) if secondary to bone marrow involvement by disease
- AST/ALT < 3 x ULN

8.2.1. Safety Review Committee

Safety considerations, including decisions to open a new dose level cohort will be made by an SRC. The SRC membership will be comprised of the sponsor's medical monitor and drug safety physician, the lead coordinating investigator (or designee), European coordinating investigator (or designee) and 2 additional physicians participating in the study and nominated by the coordinating investigators as having sufficient prior experience in early phase studies in CLL and in the use of lenalidomide in CLL. Other study team members (eg, study statistician) may also participate in SRC meetings as needed. Discussions and outcomes of SRC meetings will be documented and provided to all study investigators.

8.2.2. Dose Escalation Phase

8.2.2.1. Arm A: CC-122 Single Agent

Subjects assigned to Arm A will be administered a starting dose of 1.0 mg CC-122 orally on a 5/7-day (5 continuous days out of 7 days per week) schedule starting at Cycle 1 Day 1 with intrasubject dose escalation every 2 weeks at 0.5 mg increments at the discretion of the investigator as tolerated up to a maximum dose of 4.0 mg for a total of 24 cycles of CC-122, or until disease progression, unacceptable toxicity or discontinuation for any other reason, whichever is earlier. All treatment cycles are 28 days. Each dose will be taken in the morning with about 8 ounces of water. CC-122 may be taken up to 12 hours late if dosing has been delayed on a single day; otherwise that day's dose should be omitted.

8.2.2.2. Arm B: CC-122 in Combination with Ibrutinib

Subjects in Arm B will be administered CC-122 orally on a 5/7-day schedule.
CC-122 will be initiated on Cycle 2 Day 1 and on Day 1 of each cycle thereafter up to a maximum of 24 cycles of CC-122, or until disease progression, unacceptable toxicity or discontinuation for any other reason, whichever is earlier. Each dose will be taken in the

morning with about 8 ounces of water. CC-122 may be taken up to 12 hours late if dosing has been delayed on a single day; otherwise that day's dose should be omitted.

Dosing of ibrutinib is as described in the IMBRUVICA package insert or SmPC. Subjects will take orally three 140 mg capsules of ibrutinib daily for a total daily dose of 420 mg. Ibrutinib should be taken once daily at approximately the same time each day. The capsules should be swallowed whole with water and subjects should not open, break or chew capsules. Ibrutinib will be administered daily starting Cycle 1 Day 1 up to a maximum of 24 cycles of CC-122, or until disease progression, unacceptable toxicity or discontinuation for any other reason, whichever is earlier. For patients who discontinue CC-122 prior to 24 cycles or if patients have surpassed the 24 cycles of CC-122, Celgene will continue to provide an additional 3 cycles of ibrutinib from the investigational supply to allow time for patients to be transitioned to commercially available ibrutinib and/or other therapies at the discretion of the treating physician. Toxicity-related dose interruptions and modifications for ibrutinib are described in Section 8.2.12.2.

8.2.2.3. Arm C: CC-122 in Combination with Obinutuzumab

Subjects in Arm C will be administered CC-122 orally on a 5/7-day schedule.
CC-122 will be initiated on Cycle 1 Day 9 and on Day 1 of each cycle thereafter up to a maximum of 24 cycles of CC-122, or until disease progression, unacceptable toxicity or discontinuation for any other reason, whichever is earlier. Each dose will be taken in the morning with about 8 ounces of water. CC-122 may be taken up to 12 hours late if dosing has been delayed on a single day; otherwise that day's dose should be omitted.

Celgene will continue to provide the protocol-specified total of 6 cycles of investigational supply of obinutuzumab for ongoing patients experiencing clinical benefit. In the event CC-122 is discontinued prior to obinutuzumab, subjects may continue to receive the protocol-specified total of 6 cycles of obinutuzumab at the discretion of the treating physician. In addition, for patients that have surpassed the 24 cycles of CC-122, Celgene will continue to provide an additional 3 cycles of CC-122 to allow time for patients to be switched to commercially available therapies at the discretion of the treating physician.

Dosing of obinutuzumab is as described in the GAZYVA package insert or GAZYVARO SmPC.

Obinutuzumab will be administered as an IV infusion at a dose of 100 mg on Cycle 1 Day 1 and 900 mg on Cycle 1 Day 2 and 1000 mg on Cycle 1 Days 8 and 15. The dose of obinutuzumab on Days 1 and 2 of Cycle 1 may be adjusted per institutional practice as long as the combined dose equals 1000 mg. Obinutuzumab will be administered at a dose of 1000 mg on Day 1 of Cycles 2 through 6.

Obinutuzumab may be administered in either an inpatient or outpatient clinical setting. Full emergency resuscitation facilities must be immediately available in the event of a severe infusion reaction and subjects must be under close supervision of the investigator or appropriately trained staff during the infusions and the post-infusion period.

Please refer to the GAZYVA package insert or GAZYVARO SmPC for instructions for the preparation of each obinutuzumab dose. All transfer procedures during preparation require strict adherence to aseptic techniques. For microbiological stability, the diluted obinutuzumab

infusion solution should be used immediately. If not used immediately, the solution may be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) for up to 24 hours prior to use.

Subjects will be premedicated prior to each infusion as described in Section 9.3.3. Obinutuzumab will only be administered as a slow IV infusion through a dedicated line and **never as an IV push or bolus.** Infusion pumps should be used to control the infusion rate. Do not use an additional in-line filter because of the potential for adsorption. Infusion rates are outlined in Table 10.

After the end of the first infusion, the IV line or central venous catheter should remain in place for ≥ 2 hours to be able to administer IV treatments for infusion reactions if necessary. For subsequent infusions during Cycle 1, the IV line or central venous catheter should remain in place for at least 1 hour after the end of the infusion. For Cycles 2 and later, subjects who tolerate the infusion well without infusion reactions can have the IV line removed or the central venous catheter de-accessed immediately after the end of each infusion.

Table 10: Administered Dose and Infusion Rates for Obinutuzumab Infusions

Day of treatment cycle		Dose of obinutuzumab	Rate of infusion (in the absence of infusion reactions/ hypersensitivity during previous infusions)
Cycle 1	Day 1	100 mg	Administer at 25 mg/hr over 4 hours. Do not increase the infusion rate.
	Day 2	900 mg	Administer at 50 mg/hr. The rate of infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.
	Day 8	1000 mg	Infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.
	Day 15	1000 mg	
Cycles 2-6	Day 1	1000 mg	

Please refer to Table 14 for instructions on how to modify the dose in the event of an infusion reaction.

8.2.3. Dose Expansion Phase (Arms B and C only)

As of 05 Jul 2018, Phase 2 will not proceed.

When the Dose Escalation Phase is fully enrolled, and the evaluation completed, the preliminary RP2Ds for CC-122 in combination with ibrutinib and CC-122 in combination with obinutuzumab will be established for possible further evaluation of safety and preliminary efficacy in the Expansion Phase of the study.

Expansion cohorts at the RP2D may be conducted with a futility interim analyses as outlined in Section 10.3.1 and as shown below (Table 11 and Table 12).

Table 11: Expansion Cohort: Arm B (CC-122 in Combination with Ibrutinib)

Expansion cohort	Population[a]	N
1	Treatment-naïve, ibrutinib-naïve, and high risk CLL subjects	Futility Interim: 6 Total: 10
	R/R, ibrutinib-naïve, and high-risk CLL subjects	Futility Interim: 16 Total: 40

[a] Subjects must meet all other criteria for study entry.

Table 12: Expansion Cohort: Arm C (CC-122 in Combination with Obinutuzumab)

Expansion cohort	Population[a]	N
2	BCR PI or venetoclax resistant or intolerant subjects	Futility Interim: 17 Total: 40

[a] Subjects must meet all other criteria for study entry.

Each subject will remain on the study until disease progression, unacceptable toxicity or treatment discontinuation for any other reason. A subject may discontinue one of the study treatments and remain on study with the other treatment in compliance with all study requirements if in the judgment of the investigator the subject will derive benefit from continued study treatment. Subjects who achieve MRD negativity (in both peripheral blood and bone marrow) lasting for a minimum of 3 months in duration have the option to discontinue study treatment; study treatment in these subjects may be resumed at the time of MRD positivity (see Section 4.1).

8.2.4. Definition of Stopping Criteria for Expansion Cohort

If at any time the early DLT rate (first 28 days of CC-122 dosing during CC-122 combination therapy) exceeds 20% or the late toxicity rate (AEs identified during the first 6 cycles of CC-122 dosing necessitating dose reduction or discontinuation that are clearly not related to disease progression, medical procedure, or intercurrent illness) exceeds 33%, enrollment to that expansion cohort will be suspended pending evaluation of the safety by the SRC. The SRC may reopen enrollment into that cohort at a lower dose level that has shown to be tolerated during the dose escalation portion of the study.

In addition, an interim analysis will be performed for each expansion cohort as outlined in Section 10.3.1. If criteria as specified are not met at the time of interim analysis, enrollment to that cohort will be stopped.

8.2.5. Definition of Not Tolerated Dose (NTD)

A dose level will be considered NTD when ≥ 2 out of 6 DLT evaluable subjects in a fixed-dose cohort experience an IP-related DLT.

8.2.6. Definition of Maximum Tolerated Dose (MTD)

The MTD is defined as the last dose level below the NTD with ≤ 1 out of 6 DLT evaluable subjects experiencing DLT during the DLT evaluation period.

8.2.7. Definition of Dose Limiting Toxicity (DLT)

National Cancer Institute CTCAE Version 4.03 are used as a guide for the grading of severity of adverse events (except as otherwise specified). Dose-limiting toxicities are described below:

- A non-hematologic AE that is clearly not related to disease progression, medical procedure or intercurrent illness and that commences within 28 days of first CC-122 dose and is ≥ Grade 3 EXCEPT for:
  - Alopecia
  - Grade 3 rash of the acneiform or maculopapular type of not more than 4 days durations (with optimal medical management)
  - Grade 3 diarrhea or vomiting lasting less than 72 hours (with optimal medical management)
    - Grade 3 diarrhea requiring hospitalization and Grade 3 nausea or vomiting that required tube feeding, total parenteral nutrition, or hospitalization will be considered DLTs
- Tumor lysis syndrome (TLS), unless TLS does not progress to Grade 2 and resolves in less than 7 days with medical management
- ≥ Grade 3 tumor flare reaction (per NCI CTC AE Version 3.0)
- Laboratory abnormality that is clearly not related to disease progression, medical procedure or intercurrent illness and that commences within 28 days of first dose of CC-122 and is ≥ Grade 3 (unless otherwise specified below)
- Hematological toxicities as follows (grading as per IWCLL criteria):
  - Any febrile neutropenia
  - Grade 4 neutropenia lasting > 7 days
  - Any Grade 3 or 4 thrombocytopenia with clinically significant bleeding
  - Any cytopenia that requires dose reduction during the DLT evaluation period
- Grade 4 liver function tests or Grade 3 ALT with Grade 2 or higher bilirubin will be considered a DLT irrespective of underlying attribution
- Any AE assessed as clearly not related to disease progression, medical procedure or intercurrent illness and necessitating dose-level reduction during the DLT evaluation period.

8.2.8. Guidelines for Intrasubject Dose Escalation – Arm A

For Arm A, intrasubject dose escalation of CC-122 is permitted every 2 weeks at 0.5 mg increments at the discretion of the investigator as tolerated. Dose escalation may occur every 2 weeks if:

- The ANC is ≥ 1500 cells/mm^3 (1.5 x 10^9/L) or ≥ 1000 cells/mm^3 (1.0 x 10^9/L) if secondary to bone marrow involvement by disease
- The platelet count is ≥ 100,000 cells/mm^3 (100 x 10^9/L) or ≥ 50,000 cells/mm^3 (50 x 10^9/L) if secondary to bone marrow involvement by disease
- Any IP-related AE not requiring discontinuation has resolved to ≤ Grade 1 severity or baseline
- AST/ALT is < 3x ULN and total bilirubin is < 1.5x ULN
- Subject does not meet any other criteria for dose reduction or modification

During the every 2 week dose escalation visit, the following safety assessments will include but are not limited to:

- Hematology
- Chemistry
- Vital signs
- Tumor Flare and Tumor Lysis Monitoring
- Adverse Event and Concomitant Medication Reporting
- CC-122 Contraceptive and Risk Counseling and Education (requirement at each CC-122 dispensation visit)

8.2.9. Dose Interruptions/Modifications

Dose modifications are permitted in any cycle, including Cycle 1 and the DLT evaluation period:

- Dose reductions that occur during the DLT evaluation period will constitute a DLT, but subjects will be allowed to continue on IP at a reduced dose.
- Dose reductions are allowed for CC-122 and ibrutinib. No dose reduction is allowed for obinutuzumab, but treatment may be discontinued at the discretion of the investigator for severe infusion or allergic reactions.

8.2.9.1. General Dose Modification Guidelines

Subjects will be evaluated for AEs at each visit with the NCI CTCAE (version 4.03) used as a guide for the grading of severity, with the exception of tumor flare (NCI CTCAE version 3.0), [redacted] and laboratory abnormalities as recommended by the IWCLL guidelines for the diagnosis and treatment of chronic lymphocytic leukemia [redacted] as listed below:

Subjects experiencing related AEs or SAEs ≥ Grade 3 must interrupt dosing of the responsible IP or both IPs until resolution of the toxicity to ≤ Grade 1 or baseline severity unless as otherwise indicated in Table 14. If IP-related events do not resolve to ≤ Grade 1 or baseline severity within 28 days despite adequate medical management, the sponsor's study medical monitor should be notified.

The dose of CC-122 may be reduced successively by one level from the starting dose. There will be no more than one dose level reduction from one cycle to the next unless otherwise permitted after consultation with the sponsor medical monitor. In addition, if a subject continues to experience unacceptable toxicity after two dose reductions (with the exception of CC-122 per Table 15 where up to 3 dose reductions may be allowed for selected doses), IP will be discontinued permanently. If a dose is reduced for toxicity other than a Grade 4 non-hematological toxicity, re-escalation is permitted after the toxicity is resolved. If the toxicity recurs after re-escalation, the subject should remain at the lower dose level. Subjects who experience a Grade 4 non-hematological toxicity may not have their dose re-escalated.

For the combination of CC-122 and ibrutinib or obinutuzumab, in the event of a toxicity requiring dose modification, CC-122 should be considered for interruption and dose reduction first if possible. If the subject continues to require dose modification after a dose hold and/or reduction of CC-122 a dose interruption of obinutuzumab or ibrutinib or reduction of ibrutinib may be considered.

Dose interruptions lasting beyond 28 days should be discussed with the sponsor's study medical monitor.

If it becomes necessary to permanently stop administration of one of the IPs, continuation on the other IP will require discussion and agreement between the sponsor's study medical monitor and the investigator.

8.2.9.2. Dose Modification Guidelines

Any IP-related toxicity meeting the definition of DLT will require dose reduction or interruption. The criteria for dose reduction are listed in Table 14, should be used for dose modifications.

Chronic Grade 2 toxicity (other than specified below) may warrant dose reduction or interruption of one or both IP. Such cases should be discussed with the sponsor's medical monitor before changes are made.

Dose modification decisions for patients with cytopenia (below the lower limit of the normal range) at **baseline** will be based on the IWCLL guideline (Table 13). For patients with a normal neutrophil count, platelet count and/or hemoglobin value at baseline, the NCI CTCAE (version 4.03) will be used.

Any dose modifications must be recorded on the respective Study Drug Record eCRF.

Table 14: Dose Reduction Guidelines

Adverse Event	Grade	Action	Agent to be considered for interruption/ reduction (in descending order)
Thrombocytopenia	≥ Grade 3	• Hold all IP • Follow CBC at least every 7 days • If thrombocytopenia resolves to ≤ Grade 2, restart IP and reduce CC-122 to the next lower dose level. Ibrutinib may be restarted after thrombocytopenia resolves to ≤ Grade 1 or baseline at original dose after the 1st occurrence, and reduce by one dose level at each subsequent recurrence with a maximum of 2 dose reductions allowed. A 4th recurrence requires permanent discontinuation of ibrutinib. • Obinutuzumab should be restarted at the full dose after thrombocytopenia resolves to ≤ Grade 2, no dose reduction is allowed.	• CC-122 • Ibrutinib/obinutuzumab

Table 14: Dose Reduction Guidelines (Continued)

Adverse Event	Grade	Action	Agent to be considered for interruption/ reduction (in descending order)
Neutropenia	≥ Grade 3 with infection OR Sustained (≥ 7 days) Grade 3 OR ≥ Grade 3 associated with fever (temperature ≥ 38.5ºC) OR Grade 4	• Hold all IP • Follow CBC at least every 7 days • If neutropenia resolves to ≤ Grade 2, restart IP at the same or reduced dose level at the investigator's discretion (restarting at the same dose level is permitted only one time for those subjects with Grade 4 neutropenia. If Grade 4 neutropenia recurs, the IP dose must be reduced upon resolution). Ibrutinib may be restarted after neutropenia resolves to ≤ Grade 1 or baseline at original dose (420 mg per day) after the 1st occurrence, and reduce by one dose level (to 280 mg per day) at each subsequent recurrence with a maximum of 2 dose reductions (to 140 mg per day) allowed. A 4th recurrence requires permanent discontinuation of ibrutinib. Obinutuzumab should be restarted at the full dose after neutropenia resolves to ≤ Grade 2, no dose reduction is allowed. • Use of growth factors (G-CSF, GM-CSF) is permitted at the discretion of the investigator	• CC-122 • Ibrutinib/obinutuzumab
Troponin-T/BNP	Troponin-T > ULN with associated significant elevation in BNP or with cardiac symptoms or significant changes in ECG or LVEF	• Hold CC-122 • Cardiology evaluation • Follow troponin-T, BNP, and ECG at least every 7 days • If troponin-T and BNP stabilize and there are no other significant cardiac findings, restart CC-122 at the same or next lower dose level • Permanently discontinue CC-122 if Troponin-T > ULN with cardiac symptoms or significant changes in ECG or LVEF Please refer to Section 8.2.9.2.3 for additional guidance	• CC-122

Table 14: Dose Reduction Guidelines (Continued)

Adverse Event	Grade	Action	Agent to be considered for interruption/ reduction (in descending order)
AST/ALT/ Bilirubin	≥ Grade 3	• Hold one or more IPs at investigator's discretion • Follow labs at least every 7 days • If abnormalities resolve to ≤ Grade 1 or baseline, restart IPs and reduce CC-122 to the next lower dose level • For ibrutinib, once the toxicity has resolved to Grade 1 or baseline (recovery), ibrutinib therapy may be reinitiated at the starting dose (420 mg per day). If the toxicity reoccurs, reduce dose to 280 mg per day. A second reduction of dose to 140 mg per day may be considered as needed. If these toxicities persist or recur following two dose reductions, discontinue ibrutinib.	• CC-122 • Ibrutinib
	ALT and/or AST ≥ 3x ULN and total bilirubin > 2x ULN (potential Hy's Law)	• Hold all IPs • Conduct medical work up to determine the cause of abnormalities • Follow labs at least every 7 days until resolution to ≤Grade 1 or baseline severity for all AST, ALT and total bilirubin • In case of confirmed Hy's Law, dosing will not be resumed	
Stomatitis/Nausea/ Vomiting / Constipation	≥ Grade 3	• Hold one or more IPs at investigator's discretion if AE fails to respond to symptomatic treatment • When the toxicity resolves to ≤ Grade 1 or baseline restart both IP. • For ibrutinib, once the toxicity has resolved to Grade 1 or baseline (recovery), ibrutinib therapy may be reinitiated at the starting dose (420 mg per day). If the toxicity reoccurs, reduce dose to 280 mg per day. A second reduction of dose to 140 mg per day may be considered as needed. If these toxicities persist or recur following two dose reductions, discontinue ibrutinib.	• CC-122 • Ibrutinib

Table 14: Dose Reduction Guidelines (Continued)

Adverse Event	Grade	Action	Agent to be considered for interruption/ reduction (in descending order)
Diarrhea	≥ Grade 3	• Hold one or more IPs at the investigator's discretion • Strongly recommend to perform a colonoscopy and biopsy • When the toxicity resolves to ≤ Grade 1 restart IPs and reduce CC-122 to the next lower dose level. • For ibrutinib, once the toxicity has resolved to Grade 1 or baseline (recovery), ibrutinib therapy may be reinitiated at the starting dose (420 mg per day). If the toxicity reoccurs, reduce dose to 280 mg per day. A second reduction of dose to 140 mg per day may be considered as needed. If these toxicities persist or recur following two dose reductions, discontinue ibrutinib.	• CC-122 • Ibrutinib
Rash	≥ Grade 3	• Discontinue suspected IP for desquamating (blistering) Grade 3 or any Grade 4 rash • For maculopapular, acneiform, or pustular rashes lasting ≤ 7 days medical management is warranted	• CC-122 • Ibrutinib
Allergic Reaction or Hypersensitivity	≥ Grade 3	• For obinutuzumab: Grade 3: premedicate future doses and adjust infusion rates per standard practice Recurring Grade 3 or Grade 4: permanently discontinue • CC-122 or ibrutinib, discontinue one or more suspected IPs	• Obinutuzumab • CC-122 • Ibrutinib
Venous Thrombosis / Embolism	≥ Grade 3	• Hold CC-122 at investigator's discretion and start anticoagulation; restart CC-122 at investigator's discretion (maintain dose level) • Discontinue ibrutinib	• CC-122 • Ibrutinib
Peripheral Neuropathy (applies only to those neuropathies which begin or worsen while on study)	Newly developed ≥ Grade 3	• Hold CC-122 at investigator's discretion • When the toxicity resolves to ≤ Grade 2 or to baseline, restart CC-122 at the next lower dose level	• CC-122

Table 14: Dose Reduction Guidelines (Continued)

Adverse Event	Grade	Action	Agent to be considered for interruption/ reduction (in descending order)
Bleeding Events	≥ Grade 2	• Hold one or more IPs at investigator's discretion • When the toxicity resolves to ≤ Grade 1, restart one or more IPs	• Ibrutinib • CC-122
Tumor Lysis Syndrome	Laboratory or Grade 1 TLS	• Continue treatment at same dose level or one dose level dose reduction • Provide vigorous intravenous hydration and appropriate medical management according to the local standard of care, until correction of electrolyte abnormalities. Treat appropriately as needed to reduce hyperuricemia • Hospitalization will be at investigator's discretion	• CC-122 • Ibrutinib/obinutuzumab
	Grade 2-4	• Hold CC-122 and ibrutinib/obinutuzumab • When symptoms resolve to Grade 0, restart IPs at the next lower dose level (CC-122 and ibrutinib) or full dose (obinutuzumab). • If IPs resumed prior to the start of a subsequent cycle, a chemistry test should be performed every other day for the first week following re-initiation of IPs	
Tumor Flare Reaction (TFR)* *assessed according to NCI CTCAE Version 3.0	Grades 1-2	• Continue CC-122, maintain dose level • Initiate therapy with corticosteroids at the investigator's discretion • NSAIDs and/or narcotics may also be used as per investigator's discretion	• CC-122
	Grades 3-4	• Hold CC-122 • Initiate therapy with corticosteroids • NSAIDs and/or narcotics may also be used per investigator's discretion • When symptoms resolve ≤ Grade 1, restart CC-122 at the same dose level	
Other	≥ Grade 3	• Hold one or more IPs at investigator's discretion • When the toxicity resolves to ≤ Grade 2, restart both IPs and reduce CC-122 to the next lower dose level. Refer to package inserts or SmPCs for the approved products for dose modification instructions (ibrutinib and obinutuzumab).	--

Table 14: Dose Reduction Guidelines (Continued)

Adverse Event	Grade	Action	Agent to be considered for interruption/ reduction (in descending order)
Renal and urinary	CrCl decreased from ≥50 mL/min to 30-49 mL/min and 30% drop from baseline	• Decrease dose to next dose level	• CC-122
	CrCl decrease to < 30 mL/min	• Hold CC-122 • When CrCl improves to ≥30 mL/min, restart CC-122 at the next lower dose level	• CC-122
Surgical Procedures	Minor	• Hold one or more IPs at investigator's discretion on day of surgery • IPs may be restarted at same dose level upon recovery	• Ibrutinib • CC-122
	Major	• Hold one or more IPs for 3 to 7 days prior to surgery through 3 to 7 days post surgery • Restart IPs upon recovery and at least 3 to 7 days post surgery at the same dose level	
Infusion Reaction	Grade 1-2	• Reduce infusion rate (≤ 50% prior rate) or interrupt infusion and treat symptoms • Upon resolution, continue or resume infusion; infusion rate increments and intervals may resume at the increments and intervals as appropriate for the treatment dose if no further infusion reaction symptoms	• Obinutuzumab
	Grade 3 (severe) infusion reaction	• Interrupt infusion and manage symptoms • Upon resolution, restart infusion at ≤ 50% prior rate; infusion rate escalations can resume at the increments and intervals as appropriate for the treatment dose if no further infusion reaction symptoms • Permanently discontinue if Grade 3 or higher infusion-related symptom occurs with re-challenge	
	Grade 4 (life threatening) infusion reaction	• Stop infusion immediately; permanently discontinue	

Table 14: Dose Reduction Guidelines (Continued)

Adverse Event	Grade	Action	Agent to be considered for interruption/ reduction (in descending order)
Progressive Multifocal Leukoencephalo-pathy	All	• Permanently discontinue	• Obinutuzumab
Pneumonitis	Grade 2	• Hold one or more IPs at investigator's discretion • Once symptoms have resolved completely, CC-122 and/or ibrutinib may be restarted at the next lower dose level.	• CC-122 • Ibrutinib
	≥ Grade 3	• Discontinue one or more suspected IPs permanently	
Atrial Fibrillation	Grade 3 or 4 or persistent atrial fibrillation of any grade	• Consider the risks and benefits of ibrutinib treatment. If clinically indicated, the use of non-prohibited anticoagulants or antiplatelet agents may be considered for the thromboprophylaxis of atrial fibrillation. • If dose of ibrutinib is reduced, at the investigator's discretion, the dose of ibrutinib may be escalated after 2 cycles of a dose reduction in the absence of a recurrence of the toxicity that led to the reduction.	• Ibrutinib

Abbreviations: BNP = B-type Natriuretic Peptide; CBC = Complete Blood Count; CrCl = Creatinine Clearance; ECG = Electrocardiogram; G-CSF = Granulocyte Colony-Stimulating Factor; GM-CSF = Granulocyte-Macrophage Colony-Stimulating Factor; IP = Investigational Product; LVEF = Left Ventricular Ejection Fraction; NSAID = Non-steroidal Anti-inflammatory Drug; TLS = Tumor Lysis Syndrome; ULN = Upper Limit Normal.

8.2.9.2.3. Cardiac Laboratory Abnormalities

In addition to routine ECG monitoring in all treatment arms, additional monitoring for potential cardiac toxicity is included for subjects treated with CC-122. This includes routine monitoring of troponin-T and BNP as well as more intensive monitoring of ECGs and LVEF as described in Section 6. Elevations of troponin-T or BNP warrant further investigation including assessment of the subject for signs and symptoms of cardiac injury, consideration of a cardiology consultation, other cardiac evaluations (such as an exercise stress test, additional evaluation of LVEF, or other cardiac tests recommended by a cardiologist), and the addition of cardioprotective therapy (eg, beta blockers) as appropriate. Laboratory evaluation to assess for assay interference may also be warranted. Isolated asymptomatic elevations of troponin-T or BNP without associated ECG or LVEF changes or other cardiac findings do not require that

CC-122 dose be held. For any elevation of troponin-T > ULN associated with either significant elevation of BNP (20% increase from baseline with an absolute value > 100 pg/mL) or associated cardiac symptoms or findings, CC-122 dosing should be held and the sponsor should be notified. Additional cardiac monitoring should be performed as described in Table 14 and as medically indicated. CC-122 may be restarted at the same dose or a reduced dose, in consultation with the sponsor, based on troponin-T/BNP guidelines in Table 14 and general guidelines provided in Section 6.

8.2.9.2.4. Pneumonitis

Pneumonitis has been observed in patients taking CC-122. The diagnosis should be considered in subjects presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough, dyspnea, or interstitial pulmonary infiltrates, and in whom infectious, neoplastic and other causes are excluded by appropriate investigations. Subjects should be specifically advised to report promptly any new or worsening respiratory symptoms they experience.

Those with radiological features suggestive of non-infectious pneumonitis but with minimal (Grade 1) symptoms may continue CC-122 without dose alteration. For drug-related Grade 2 pneumonitis, CC-122 treatment should be interrupted and corticosteroids may be indicated. Once symptoms have resolved completely, CC-122 may be reintroduced at the next lower dose level. For drug-related Grade 3 or 4 pneumonitis CC-122 must be permanently discontinued and corticosteroids are recommended until clinical symptoms have resolved.

[redacted]

8.2.10. Management of Select AEs While Receiving Obinutuzumab

8.2.10.1. Infusion-Related Reactions (IRRs)

Two-thirds of patients experienced IRRs with the first infusion of obinutuzumab; reactions can also occur with subsequent infusions, but the frequency is lower (GAZYVA, GAZYVARO). Infusion reactions typically occur within 24 hours of receiving obinutuzumab. Symptoms may include anaphylaxis, acute life-threatening respiratory symptoms, hypotension, tachycardia, dyspnea, bronchospasms, larynx and throat irritation, wheezing, and laryngeal edema. Additional potential symptoms include nausea, vomiting, diarrhea, hypertension, flushing, skin rash, urticaria, headache, pyrexia, and chills.

To minimize the potential for these reactions, premedication is administered as described in Section 9.3.3. Full emergency resuscitation facilities should be immediately available in the event of a severe and life-threatening infusion reaction and subjects should be under close supervision of the investigator or appropriately trained staff during the infusions. Medical

management of infusion reactions should be instituted according to standard medical practice using glucocorticoids, epinephrine, oxygen, intravenous fluids and other medications as medically indicated. Subsequent infusions should be administered with appropriate premedications as in Section 9.3.3.

Subjects with pre-existing cardiac or pulmonary conditions should be monitored more frequently throughout the infusion and after the infusion. Hypotension may occur and investigators should consider withholding antihypertensive agents (for subjects not at risk for hypertensive crisis) for 12 hours prior to, during the infusion, and for 1 hour after the infusion until blood pressure is stable.

8.2.10.2. Progressive Multifocal Leukoencephalopathy

John Cunningham (JC) virus infection resulting in progressive multifocal leukoencephalopathy (PML), which can be fatal, has been observed in patients treated with obinutuzumab. Subjects with new onset or changes to pre-existing neurologic manifestations should be evaluated for PML. The symptoms of PML are unspecific and can vary depending on the affected region of the brain. Motor symptoms with corticospinal tract findings (eg, muscular weakness, paralysis, and sensory disturbances), sensory abnormalities, cerebellar symptoms, and visual field defects are common. Some signs/symptoms regarded as "cortical" (eg, aphasia or visual-spatial disorientation) may occur. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture [redacted] Obinutuzumab and CC-122 should be discontinued in subjects who develop PML. The subject should be referred to a neurologist for the evaluation and treatment of PML.

8.2.10.3. Neutropenia, Thrombocytopenia, and Anemia

[redacted]

Severe and life-threatening thrombocytopenia, including acute thrombocytopenia (occurring within 24 hours after the infusion), has been observed during treatment with obinutuzumab. Fatal hemorrhagic events have also been reported in Cycle 1 in patients treated with obinutuzumab (GAZYVA, GAZYVARO). A clear relationship between thrombocytopenia and hemorrhagic events has not been established. Subjects should be closely monitored for thrombocytopenia, especially during the first cycle. Regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe or life-threatening thrombocytopenia. Transfusion of blood products (ie, platelet transfusion) according to institutional practice is at the discretion of the treating physician. Use of all concomitant therapies, which could possibly worsen thrombocytopenia-related events such as platelet inhibitors and anticoagulants, should also be taken into consideration, especially during the first cycle.

Hematopoietic growth factors or other hematologic support, such as erythropoietin, darbepoetin, granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), RBC- or platelet- transfusions are allowed in the study with therapeutic intent.

Therapeutic use of G-CSF is allowed at any time for subjects experiencing Grade 3 or 4 neutropenia or any grade febrile neutropenia. Prophylactic use of granulocyte (or granulocyte-macrophage) growth factors is not allowed during Cycle 1.

8.2.10.4. Gastrointestinal (GI) Perforation

Cases of gastrointestinal perforation have been reported in patients receiving obinutuzumab (GAZYVA, GAZYVARO) mainly in NHL. Monitor patients with GI involvement for GI perforation.

8.2.11. Management of Select AEs While Receiving Ibrutinib

Fatal bleeding events have occurred in patients treated with ibrutinib (IMBRUVICA). Grade 3 or higher bleeding events (subdural hematoma, gastrointestinal bleeding, hematuria and post procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with IMBRUVICA. The mechanism for the bleeding events is not well understood. IMBRUVICA may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies.

Consider the benefit-risk of withholding IMBRUVICA for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding.

Inform subjects of the possibility of bleeding, and report any signs or symptoms (blood in stools or urine, prolonged or uncontrolled bleeding). Inform the subject that IMBRUVICA may need to be interrupted for medical or dental procedures.

Subjects should be closely monitored for hemorrhagic events. Regular laboratory tests should be performed until the event resolves, and dose delays should be considered in the event of ≥ Grade 2 hemorrhage (Table 14). Transfusion of blood products (ie, RBC- or platelet- transfusions) according to institutional practice is at the discretion of the treating physician.

For any subjects receiving ibrutinib (Arm B), major hemorrhages as defined in Section 11.1 are considered adverse events of special interest and must be reported on the Serious Adverse Event Report Form using the "Important Medical Event" as the seriousness criteria and sent via email or fax to Celgene and/or designee, within 24 hours of awareness (see Section 11.5.1).

8.2.11.1. Interstitial Lung Disease (ILD)

Cases of ILD have been reported in patients treated with ibrutinib. Monitor patients for pulmonary symptoms indicative of ILD. Should symptoms develop, follow the protocol dose modification guidelines as outlined in Table 16.

8.2.12. Dose Reduction Steps

If a subject develops toxicity, the dose of CC-122 may be reduced as outlined in Table 15 and ibrutinib as outlined in Table 16.

8.2.12.1. CC-122 Dose Reduction Steps

Recommendations for dose reduction steps for CC-122 are presented in Table 15. Up to 3 dose reductions will be permitted for patients who receive an initial starting dose of 3.0 mg, 3.5 mg or 4.0 mg, provided data from the fixed-dose cohorts during the escalation phase demonstrates that

1.5 mg, 2.0 mg and 2.5 mg are active (i.e. at least 1 objective response (CR or PR/PRL) was observed).

Table 15: CC-122 Dose Reduction Steps

Current Dose	0.5 mg	1.0 mg	1.5 mg	2.0 mg	2.5 mg	3.0 mg	3.5 mg	4.0 mg
Dose Reduction 1	0.25 mg	0.5 mg	1.0 mg	1.5 mg	2.0 mg	2.5 mg	3.0 mg	3.5 mg
Dose Reduction 2	0.1 mg	0.25 mg	0.5 mg	1.0 mg	1.5 mg	2.0 mg	2.5 mg	3.0 mg
Dose Reduction 3	D/C	D/C	D/C	D/C	D/C	1.5 mg	2.0 mg	2.5 mg

Abbreviation: D/C = Discontinue.

8.2.12.2. Ibrutinib Dose Reduction Steps

Ibrutinib dose reduction steps are shown in Table 16.

Table 16: Ibrutinib Dose Reduction Steps

Non-Hematologic Adverse Events	
Toxicity Occurrence	**Action to be Taken**
First	Withhold ibrutinib until recovery to Grade ≤ 1 or baseline; may restart at original dose level, 420 mg daily
Second	Withhold ibrutinib until recovery to Grade ≤ 1 or baseline; may restart at 1 dose level lower, 280 mg daily
Third	Withhold ibrutinib until recovery to Grade ≤ 1 or baseline; may restart at 1 dose level lower, 140 mg daily
Fourth	Discontinue Ibrutinib

8.2.12.3. Dose Modification Guidelines for Obinutuzumab

There is no allowable dose reduction schedule for obinutuzumab. In the event of toxicities or adverse events, dose modification should be based on Section 8.2.9.1.

8.2.13. Overdose

Overdose, as defined for this protocol, refers to CC-122, ibrutinib and obinutuzumab dosing only.

On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of CC-122 or ibrutinib assigned to a given subject, regardless of any associated adverse events or sequelae.

- PO any amount over the protocol-specified dose
- IV 10% over the protocol-specified dose

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

On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form. See Section 11 for the reporting of AEs associated with overdose.

8.3. Method of Treatment Assignment

As of 05 Jul 2018, enrollment of new subjects into Phase 1 has been discontinued.

Assignment of subjects to Arms A, B, or C will be based on current open dose levels, investigator choice, and available slots.

An interactive web response system (IWRS) will be used to track subject assignments to the treatment arms and dose levels.

8.4. Packaging and Labeling

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

8.5. Investigational Product Accountability and Disposal

The investigator(s) is responsible for taking an inventory of each shipment of IP received and comparing it with the accompanying IP shipping order form. The investigator(s) will verify the accuracy of the information on the form to register the IP received at the site and retain a copy of the form in the study file.

At the study site, all investigational IP will be stored in a locked, safe area to prevent unauthorized access. The IP should be stored as directed on the package label.

Celgene (or designee) will review with the investigator and relevant site personnel the process for Investigational Product return, disposal, and/or destruction including responsibilities for the site versus Celgene (or designee).

8.6. Investigational Product Compliance

Subjects will return all IP at the Day 1 scheduled visit of each cycle to assess treatment compliance. Subjects must miss no more than 5 scheduled doses of IP during the DLT evaluation period (eg, forget to take or lose their IP; or if discontinued early due to progressive disease) to be considered evaluable for DLT, unless the missed doses were due to IP-related AE(s), in which case they remain evaluable for DLT. During subsequent cycles, a subject will be considered compliant with each IP and overall if the IPs taken are $\geq$ 80% to $\leq$ 120% of the assigned dosage. IP accountability will be evaluated on Day 1 of each cycle; full and/or partial bottles may be re-dispensed once IP accountability has been performed.

10. STATISTICAL ANALYSES

10.1. Overview

The primary objectives of this Phase 1/2 Study are to determine the safety of single agent CC-122 and the safety, tolerability, and RP2D of CC-122 when administered in combination with ibrutinib and in combination with obinutuzumab to subjects with CLL/SLL. The secondary objectives are to evaluate the PK profiles of subjects administered CC-122 in combination with ibrutinib and in combination with obinutuzumab, to determine ibrutinib concentrations when given alone and in combination with CC-122, and to evaluate the preliminary efficacy of CC-122 at selected dose levels/regimens.

As of 05 Jul 2018, enrollment of new subjects into Phase 1 has been discontinued. Subjects already enrolled who are receiving clinical benefit in the opinion of the treating investigator may continue to receive study treatment up to a maximum of 24 cycles of CC-122.

In the following, statistical analyses will be performed by study arm, dose level and visit cycle as needed or applicable.

10.2. Study Population Definitions

For the purpose of statistical analysis and data presentation, the study populations are defined as follows:

- Safety Population – all subjects who take at least one dose of IP.
- Dose-Limiting Toxicity Evaluable Population –
  - Arm A: all subjects who completed at least one cycle of treatment and did not miss more than 5 days of CC-122 dosing during the first cycle are to be considered evaluable for DLT, unless the missed doses were due to IP related AE(s) or the cycle was not completed due to a DLT, in which case they remain evaluable for DLT.
  - Arm B: all subjects who completed at least one cycle of CC-122 (Cycle 2 Day 1 through Cycle 2 Day 28) and did not miss more than 5 days of CC-122 treatment are to be considered evaluable for DLT, unless the missed doses were due to IP related AE(s) or the cycle was not completed due to a DLT, in which case they remain evaluable for DLT.
  - Arm C: all subjects who completed at least one cycle of CC-122 (Cycle 1 Day 9 through Cycle 2 Day 8) and did not miss more than 5 days of CC-122 treatment are to be considered evaluable for DLT, unless the missed doses were due to IP related AE(s) or the cycle was not completed due to a DLT, in which case they remain evaluable for DLT.
- Efficacy Evaluable (EE) Population – all subjects who complete at least one cycle of their assigned treatment regimen, and have a baseline and at least one post-baseline efficacy assessment.
- Pharmacokinetic Population – all subjects who have at least 1 measurable CC-122 and/or ibrutinib concentration datum.

10.3. Sample Size and Power Considerations

During the Dose Escalation Phase of the study, an intrasubject dose escalation schedule and standard "3 + 3" dose escalation design will be used to identify initial toxicities and safety of single agent CC-122 and to determine the MTD of the combination treatments. The final number of subjects needed in the Dose Escalation Phase depends on number of DLTs observed within each cohort. Non-DLT evaluable subjects withdrawn prior to completion of the DLT evaluation period due to reasons other than DLT will be replaced. After the MTD and preliminary RP2D have been determined for CC-122 in combination with ibrutinib and CC-122 in combination with obinutuzumab, 2 additional cohorts may be enrolled to further evaluate the safety and efficacy of the combination therapy in specific subject populations at the preliminary RP2D in the Expansion Phase.

10.3.1. Expansion Cohorts

As of 05 Jul 2018, Phase 2 will not proceed.

The sample size of 50 subjects/cohort for Expansion Cohort 1 and 40 subjects/cohort for Expansion Cohort 2 are not based on formal statistical calculation to have adequate power for hypothesis testing. Rather it is to provide additional efficacy and safety information beyond the limited number of subjects in the Dose Escalation Phase. To reduce the risk that subjects exposure to less efficient IP, a futility interim analysis will be conducted for each expansion cohort.

Estimates of expected response rate were calculated for each patient population to be evaluated in the expansion cohorts based on currently available published data, when available:

- Arm B, Expansion Cohort 1, will evaluate subjects with high risk CLL (n=10 for TN CLL, n=40 for R/R CLL). A design with futility interim will be applied to both TN (n=10) and R/R CLL cohorts (n=40). An estimated ORR of 97% (including both PR and PRL) and CR of 12% is projected for single agent ibrutinib in TN CLL with 17p-/TP53 mutation (Farooqui, 2015). An estimated ORR of 60% is projected based on single agent ibrutinib data in R/R high risk CLL. Four studies with ibrutinib in 17p-/TP53 mutation positive R/R CLL reported response rates ranging from 40% to 71% (Pollyea, 2014; IMBRUVICA; Preetesh, 2015; Farooqui, 2015). The total number of responders was divided by the total number of subjects from the four studies to estimate an ORR of 60% for this cohort.
- Arm C, Expansion Cohort 2, will evaluate patients who are resistant to or intolerant of prior ibrutinib/idelalisib/venetoclax or alternate BTK or PI3K inhibitors. Limited data is available on the response of patients post-treatment failure with ibrutinib and idelalisib. One study reported 25% to 76% response rates with kinase inhibitors (idelalisib or ibrutinib if not previously experienced) or non-kinase inhibitors (anti-CD20 antibody, chemotherapy, BCL-2 inhibitor, etc) in patients who were resistant or intolerant of idelalisib or ibrutinib (Mato, 2015), therefore an ORR of 50% is projected for this cohort.

Based on the above assumptions, a design with a futility interim analysis will be applied in the expansion cohorts:

- Arm B, TN CLL cohort: Considering 97% of TN CLL patients are expected to have a response with monotherapy ibrutinib, the stopping rule will be based on either excessive toxicity or lack of efficacy. Specifically, the enrollment to the TN CLL cohort will be stopped if ≥ 2 DLTs are observed among the first ≤ 6 patients or if < 5 responses (CR, PR/PRL) are observed among the first 6 efficacy evaluable subjects.
- Arm B, Expansion Cohort 1, the hypotheses for the true ORR to be tested are $p \leq 0.5$ versus $p \geq 0.7$. An interim analysis for futility purpose will be conducted on the first 16 efficacy evaluable subjects. If there are at least 10 responders, the cohort will be completed to include a total of 40 subjects. The probability of early termination of the study at the interim analysis is not less than 0.77 if the true ORR rate is 0.5 or less. If the true ORR is 0.7 or greater and there are at least 10 responders at the futility interim, the expected lower boundary of exact 95% confidence interval is larger than 0.5.
- Arm C, Expansion Cohort 2, the hypotheses for the true ORR to be tested are $p \leq 0.4$ versus $p \geq 0.6$. A futility interim analysis will be conducted when there are 17 subjects that are efficacy evaluable. If there are at least 9 responders, the trial will be completed to include a total of 40 subjects. The probability of early termination of the study at the interim analysis is not less than 0.80 if the true ORR rate is 0.4 or less. If the true ORR is 0.6 or greater and there are at least 9 responders at the futility interim, the expected lower boundary of exact 95% confidence interval is larger than 0.4.

10.4. Background and Demographic Characteristics

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

10.5. Subject Disposition

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

10.6. Efficacy Analysis

All efficacy evaluable subjects will be included for efficacy analysis.

Response, including evaluation of MRD, will be assessed by IWCLL guidelines for diagnosis and treatment of CLL [redacted] with modifications. The response rate based on the best response during the treatment period and the relative proportions in each response category will be examined. Distributions of the responses into the response categories (CR, CRi, nPR, PR, PRL, SD, PD) will be provided for each arm and dose level. Response at selected time points (eg, end of Cycle 3, end of Cycle 6, end of Cycle 12, end of treatment) may also be provided for each arm and dose level. Overall response rate (CR + CRi + PR + nPR + PRL [PRL is applicable to Arm B only]) and MRD negativity rate together with

confidence intervals will be provided for each treatment arm and dose level. For subjects having brief signs of progression while off CC-122, or combination of this with ibrutinib or obinutuzumab, which resolves with reinitiation of therapy, this will not be considered progression.

Duration of response is defined as the time from first PRL [applicable to Arm B only], nPR, PR, CRi, or CR to PD. Duration of response will be censored at the last date that the patient was known to be progression-free for: 1) patients who have not progressed at the time of analysis; 2) patients who have withdrawn consent or are lost to follow-up prior to documentation of progression. Duration of response will be analyzed using the Kaplan-Meier method. Median duration of response along with two-sided confidence interval will be provided for each treatment arm and dose level.

Progression-free survival is calculated as the time from first IP dose to the first documented progression or death due to any cause during or after the treatment period, whichever occurs first. Median PFS will be estimated using Kaplan-Meier estimates and the 95% confidence intervals (CI) will be computed by the method of Klein and Moeschberger [redacted] with log-log transformation with each treatment arm and dose level.

10.7. Safety Analysis

All subjects who receive at least one dose of any assigned IP will be included in the safety analyses. Adverse events, vital sign measurements, physical exam findings, clinical laboratory information, ECG interpretations, LVEF assessments, pregnancy tests for FCBP, concomitant medications and procedures will be tabulated and summarized by study phase, treatment arm, and dose level, as appropriate.

In the Dose Escalation Phase, during the 28 days following initiation of CC-122, DLTs and all available safety information will be reviewed on an ongoing basis by the investigators and sponsor and summarized at the conclusion of each dose level for each treatment arm. Treatment arms will be evaluated independently. After completion of each dosing cohort the SRC will review the summarized data to determine the next step. Dose-limiting toxicity occurrence will be summarized by treatment arm and dose level as appropriate.

Adverse events observed will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). The severity or intensity of adverse events will be graded according to the CTCAE version 4.03 unless otherwise specified.

The frequency of AEs will be tabulated by MedDRA SOC and PT. In the by-subject analysis, a subject having the same event more than once will be counted only once. Adverse events leading to discontinuation from treatment, events classified as CTCAE Grade 3 or higher, IP-related events, and serious AEs will be tabulated and listed separately. By-subject listings of all AEs, serious AEs, and their attributes will be provided.

Clinical laboratory data will be summarized. Laboratory data will be graded according to CTCAE version 4.03 criteria for select analytes unless otherwise specified. The frequencies of the worst severity grade observed during treatment will be displayed in cross-tabulations by screening status.

Vital signs, ECG data and LVEF data will be summarized by cross-tabulations presenting normal and abnormal values by number of subjects at pre- and post-IP initiation.

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

10.8. Interim Analysis

Futility interim analysis is planned for the expansion cohorts as described in Section 10.3.1.

10.9. Other Topics

10.9.1. Assessment of Pharmacokinetics

The PK population includes all subjects who have at least 1 measurable CC-122 and/or ibrutinib plasma concentration datum. The evaluable subjects in the PK population will be included in the PK data analysis.

Noncompartmental analysis will be performed on the drug concentration data for subjects with intensive PK sampling. Pharmacokinetic parameters include, but are not limited to, the following:

C_{max}	Peak (maximum) drug plasma concentration
T_{max}	Time to peak (maximum) drug concentration
AUCt	Area under the concentration -time curve calculated to the last observable concentration at time t
AUC∞	Area under the plasma concentration-time curve from time zero to infinity,
AUCτ	Area under the plasma concentration-time curve during the dosing interval (τ) at steady state
t½	Terminal elimination half-life
CL/F	Apparent clearance of drug from plasma
Vz/F	Apparent volume of distribution during the terminal phase after extravascular administration
Rac	Accumulation ratio based on AUC after multiple dose administration relative to single dose administration

Details of statistical analyses of drug concentration data and PK parameters are included in the statistical analysis plan.

[redacted]

11. ADVERSE EVENTS

11.1. Monitoring, Recording and Reporting of Adverse Events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 8.2.9), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose eCRF (see Section 8.2.13 for the definition of overdose). Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE on the AE eCRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE eCRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and eCRF but should not be reported as an SAE itself.

In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for CC-122, obinutuzumab, or ibrutinib overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

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

All AEs will be recorded by the investigator from the time the subject signs informed consent until 28 days after the last dose of IP and those SAEs made known to the investigator at any time thereafter that are suspected of being related to IP. Adverse Events and serious adverse events (SAEs) will be recorded on the AE page of the eCRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours of the investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

Additionally, for any subject receiving obinutuzumab, the site will simultaneously send the SAE Report Form to Celgene and Hoffmann-La Roche within the same timeframe and method.

11.1.1. Adverse Events of Special Interest

Specific adverse events, or groups of adverse events, will be followed as part of safety monitoring activities by the Sponsor.

11.1.1.1. Major Hemorrhage (Arm B)

For any subjects receiving ibrutinib (Arm B), major hemorrhages as defined below are considered adverse events of special interest and must be reported on the Serious Adverse Event Report Form using the "Important Medical Event" as the seriousness criteria and sent via email or fax to Celgene and/or designee, within 24 hours of awareness (see Section 11.5.1).

Major hemorrhage is defined as any of the following:

- Any treatment-emergent hemorrhagic adverse events of Grade 3 or higher*
- Any treatment-emergent serious adverse events of bleeding of any grade
- Any treatment-emergent central nervous system hemorrhage/hematoma of any grade

*All hemorrhagic events requiring transfusion of red blood cells should be reported as a Grade 3 or higher AE per CTCAE.

[redacted]

11.2. Evaluation of Adverse Events

A qualified investigator will evaluate all adverse events as to:

11.2.1. Seriousness

An SAE is any AE occurring at any dose that:

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

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above.

Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

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

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (ie, planned prior to starting of treatment on study); must be documented in the source document and the eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of or an elective procedure for a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the eCRF and the SAE Report Form must be completed.

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

11.2.2. Severity / Intensity

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

The severity / intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of the CTCAE Version 4.03 with the exception of TFR (NCI CTCAE version 3.0), [redacted] and laboratory abnormalities as recommended by the IWCLL guidelines for the diagnosis and treatment of CL [redacted]

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

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

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

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

11.2.3. Causality

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

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

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

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

11.2.4. Duration

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

11.2.5. Action Taken

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

11.2.6. Outcome

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

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

11.3. Abnormal Laboratory Values

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

- results in discontinuation from the study; or
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or
- considered clinically significant by the investigator, regardless of the severity.

Grade 3/4 laboratory abnormalities will be reported as adverse events independent of associated signs or symptoms, if it requires treatment, modification or interruption of IP dose, or any other therapeutic intervention, or results in discontinuation from the study. The associated signs and symptoms will be considered as additional event terms and graded according to their own criteria.

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

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

11.4. Pregnancy

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

11.4.1. Females of Childbearing Potential

The following are considered immediately reportable events:

- Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on study drugs, or within at least 28 days of the subject's last dose of CC-122.

- Pregnancies of female subjects occurring while the subject is on study drug, or within at least 18 months after the subject's last dose of obinutuzumab.

IP is to be discontinued immediately and the subject instructed to return any unused portion of the IP to the investigator as applicable. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The exposure of any pregnant female (eg, caregiver or pharmacist) to CC-122 is also an immediately reportable event.

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

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

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

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

Additionally, for any subject receiving obinutuzumab, the site will simultaneously send the SAE Report Form to Celgene and Hoffmann-La Roche within the same timeframe and method.

11.4.2. Male Subjects

If a female partner of a male subject taking IP becomes pregnant, the male subject taking IP should notify the investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

11.5. Reporting of Serious Adverse Events

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

The investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent until 28 days after the last dose of IP) or any SAE made known to the investigator at any time thereafter that are suspected of being related to IP. Serious AEs occurring prior to treatment (after signing the ICF) will be captured.

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

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

11.5.1. Adverse Events of Special Interest

Specific adverse events, or groups of adverse events, will be followed as part of safety monitoring activities by the Sponsor.

11.5.1.1. Major Hemorrhage (Arm B)

For any subjects receiving ibrutinib (Arm B), major hemorrhages as defined in Section 11.1.1.1 are considered adverse events of special interest and must be reported on the Serious Adverse Event Report Form using the "Important Medical Event" as the seriousness criteria and sent via email or fax to Celgene and/or designee, within 24 hours of awareness.

[redacted]

11.6. Safety Queries

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

11.7. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to CC-122 based on the IB.

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

For countries within the European Economic Area (EEA), Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, SUSARs in accordance with Directive 2001/20/EC and the Detailed

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

For the purpose of regulatory reporting in the EEA, Celgene Drug Safety will determine the expectedness of events suspected of being related to ibrutinib based on the EU SmPC and to obinutuzumab based on the IB.

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

Celgene or its authorized representative shall notify the investigator of the following information:

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

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

The investigator must keep copies of all pertinent safety information on file including correspondence with Celgene and the IRB/EC. (See Section 15.3 for record retention information.)

Celgene Drug Safety Contact Information:

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

12. DISCONTINUATIONS

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

- Adverse event
- Disease progression
- Withdrawal by subject
- Death
- Lost to follow-up
- Protocol violation
- Start of a new anti-CLL therapy (with the exception of rituximab for the treatment of autoimmune hemolytic anemia)
- Upon completion of a maximum of 24 cycles of CC-122
- For subjects on Arm B, subjects who have discontinued CC-122 prior to the maximum of 24 cycles and have received an additional 3 cycles of investigational supply of ibrutinib

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

The decision to discontinue a subject remains the responsibility of the treating physician, which will not be delayed or refused by the sponsor. However, prior to discontinuing a subject, the investigator may contact the medical monitor and forward appropriate supporting documents for review and discussion.

13. EMERGENCY PROCEDURES

13.1. Emergency Contact

In emergency situations, the investigator should contact the responsible clinical research physician/medical monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

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

Note: The back-up 24 hour global emergency contact call center should only be used if you are not able to reach the clinical research physician(s) or medical monitor or designee for emergency calls.

13.2. Emergency Identification of Investigational Products

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

14. REGULATORY CONSIDERATIONS

14.1. Good Clinical Practice

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

14.2. Investigator Responsibilities

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

The investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions. The investigator should maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

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

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

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

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

14.3. Subject Information and Informed Consent

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

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

14.4. Confidentiality

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

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

14.5. Protocol Amendments

Any amendment to this protocol must be approved by the Celgene clinical research physician/medical monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

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

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

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

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

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

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

14.7. Ongoing Information for Institutional Review Board/Ethics Committee

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

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

14.8. Closure of the Study

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

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

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;

- Falsification of records;
- Failure to adhere to the study protocol.

15. DATA HANDLING AND RECORDKEEPING

15.1. Data/Documents

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

15.2. Data Management

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

15.3. Record Retention

Essential documents must be retained by the investigator for a minimum of 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 IP. The investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed informed consent documents for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the investigator, Celgene, and their authorized representative(s);
- List of sub-investigators and other appropriately qualified persons to whom the investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);

- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

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

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

16. QUALITY CONTROL AND QUALITY ASSURANCE

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

16.1. Study Monitoring and Source Document Verification

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the investigator and the staff at a study initiation visit and/or at an investigator meeting. 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/SAEs with the investigator. Monitoring will include on-site visits with the investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, investigational product storage area, eCRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative in accordance with the Study Monitoring Plan.

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

16.2. Audits and Inspections

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

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

16.3. Product Quality Complaint

A Product Quality Complaint (PQC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, purity, or performance of any drug product manufactured by or on behalf of Celgene Corporation after it is released for distribution. PQCs may reduce the usability of the product for its intended function or affect performance of the product and therefore pose a significant risk to the patient. Examples of PQCs include (but are not limited to): mixed product, mislabeling, lack of effect, seal/packaging breach, product missing/short/overage, contamination, suspected falsified, tampered, diverted or stolen material, and general product/packaging damage. If you become aware of a suspected PQC, you are obligated to report the issue immediately. [redacted]