Statistical Analysis Plan for

Official Title of Study

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

NCT02406742

29-June-2020

STATISTICAL ANALYSIS PLAN

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

STUDY DRUG: **CC-122**

PROTOCOL NUMBER: **CC-122-CLL-001**

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Printed Name _____ Date _____

Lead Product Safety Physician

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Printed Name _____ Date _____

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Printed Name _____ Date _____

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Signature _____

Printed Name _____ Date _____

1. LIST OF ABBREVIATIONS

Table 1: Abbreviations and Specialist Terms

Abbreviation or specialist term	Explanation
5PS	5-point scale
AE	Adverse Event
ALC	Absolute Lymphocyte Count
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under Concentration
BCR PI	B-Cell Receptor Pathway Inhibitor
BQL	Below the Quantification Limit
BMI	Body Mass Index
BNP	B-type Natriuretic Peptide
bpm	beats per minute
BPM	Breaths per Minute
BSA	Body Surface Area
BTK	Bruton's tyrosine kinase
BUN	Blood urea nitrogen
CBC	Complete Blood Count
CI	Confidence Interval
CIRS	Cumulative Illness Rating Scale
CL/F	Apparent clearance of drug from plasma
CLL	Chronic Lymphocytic Leukemia
C_{max}	Peak (maximum) drug plasma concentration
CR	Complete Response
CRF	Case Report Form
CRi	Complete Response with incomplete marrow recovery
CTCAE	Common Terminology Criteria for Adverse Events
CT	Computerized Tomography

Table 1: Abbreviations and Specialist Terms (continued)

Abbreviation or specialist term	Explanation
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
DoR	Duration of Response
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EE	Efficacy Evaluable
EOT	End of Treatment
Esc	Escalation Level
FISH	Fluorescent In Situ Hybridization
FDG	Fluorodeoxyglucose
fT4	Free T4
G-CSF	Granulocyte Colony-Stimulating Factor
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
HBsAg	Hepatitis B surface Antigen
anti-HBc	Hepatitis B core antibody
HCV	Hepatitis C Virus
HGB	Hemoglobin
IFN-γ	Interferon-gamma
Ig	Immunoglobulin
IgVH	Immunoglobulin Heavy Chain
IL	Interleukin
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
LD	Longest Diameter
LDH	Lactate Dehydrogenase

Table 1: Abbreviations and Specialist Terms (continued)

Abbreviation or specialist term	Explanation
LLOQ	Low Limit Of Quantification
LOD	Limit Of Detection
LPD	Longest Perpendicular Diameter
LVD	Longest Vertical Dimension
LVEF	Left Ventricular Ejection Fraction
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Affairs
Min	Minimum
MRD	Minimum Residual Disease
MTD	Maximum Tolerated Dose
NCA	Non-compartmental analysis
NCI	National Cancer Institute
nPR	nodular Partial Response
NTD	Non-Tolerated Dose
ORR	Objective Response Rate
PBMC	Peripheral blood mononuclear cell
PD	Progressive Disease
PDwH	PD with histologic transformation
PDw/oH	PD without histologic transformation
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PK	Pharmacokinetic
PR	Partial Response
PRL	Partial Response with Lymphocytosis
PT	Preferred Term
PTT	Partial Thromboplastin Time
QD	Daily Dose
QNS	Quantity Not Sufficient
QTc	Corrected QT Interval
QTcB	Bazett Corrected QT Interval
QTcF	Fridericia Corrected QT Interval

Table 1: Abbreviations and Specialist Terms (continued)

Abbreviation or specialist term	Explanation
Rac	Accumulation Ratio
RBC	Red Blood Cell
RNA	Ribonucleic Acid
RP2D	Recommended Phase 2 Dose
RR	R wave to R wave interval
R/R	Relapsed/Refractory
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Stable Disease
SE	Standard Error
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamate pyruvic transaminase
SLL	Small Lymphocytic Lymphoma
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
SPD	Sum of the product of the Perpendicular Diameters for multiple lesions
SRC	Safety Review Committee
StdDev	Standard Deviation
$t_{½}$	Terminal elimination half-life
TEAE	Treatment Emergent Adverse Event
TFR	Tumor Flare Reaction
TLS	Tumor Lysis Syndrome
T_{max}	Time to peak (maximum) drug concentration
TN	Treatment Naïve
TNF	Tumor Necrosis Factor
TSH	Thyroid Stimulating Hormone
Vz/F	Apparent volume of distribution during the terminal phase after extravascular administration
WBC	White Blood Cell
WHO	World Health Organization

Table 1: Abbreviations and Specialist Terms (continued)

Abbreviation or specialist term	Explanation
WHODrug	World Health Organization Drug Dictionary
ZAP 70	Zeta-Chain-Associated Protein Kinase

2. INTRODUCTION

This statistical analysis plan (SAP) describes the analyses and data presentations for Celgene's protocol amendment 7 "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" that was issued on 27 July 2018.

The main focus of the dose escalation phase of the study CC-122-CLL-001 is to determine the safety of single agent CC-122 (Arm A) and the safety and tolerability of CC-122 when administered in combination with ibrutinib (Arm B) and when administered in combination with obinutuzumab (Arm C), and to define the Non-Tolerated Dose (NTD), Maximum Tolerated Dose (MTD), and the Recommended Phase 2 Dose (RP2D) of CC-122 for each of those combinations. The RP2D may be the MTD or lower dose depending on tolerability, the pharmacokinetic (PK) profile, and the pharmacodynamic profile observed. The Safety Review Committee (SRC) will identify a preliminary RP2D for Arms B and C based on an integrated assessment of the safety, available PK, pharmacodynamics data and preliminary efficacy information. The RP2D selected will not exceed the MTD from the dose escalation cohorts.

The principal objectives of the dose expansion phase are to further assess the safety profile and to provide preliminary efficacy information of CC-122 in combination with ibrutinib, and CC-122 in combination with obinutuzumab in subjects with Relapsed/Refractory (R/R) chronic lymphocytic leukemia (CLL)/Small Lymphocytic Lymphoma (SLL). Since the Phase 2 dose expansion phase will not proceed per Protocol Amendment 7, further characterization of the MTD and RP2D in the dose expansion phase will not be conducted.

The purpose of this SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to the analysis of study data prior to database lock. This SAP contains definitions for the analysis populations and derived variables, as well as the description of the strategy, rationale and statistical techniques to be used to achieve the objectives of the dose escalation of the study. The analysis for dose expansion will not be conducted and is not included in this SAP.

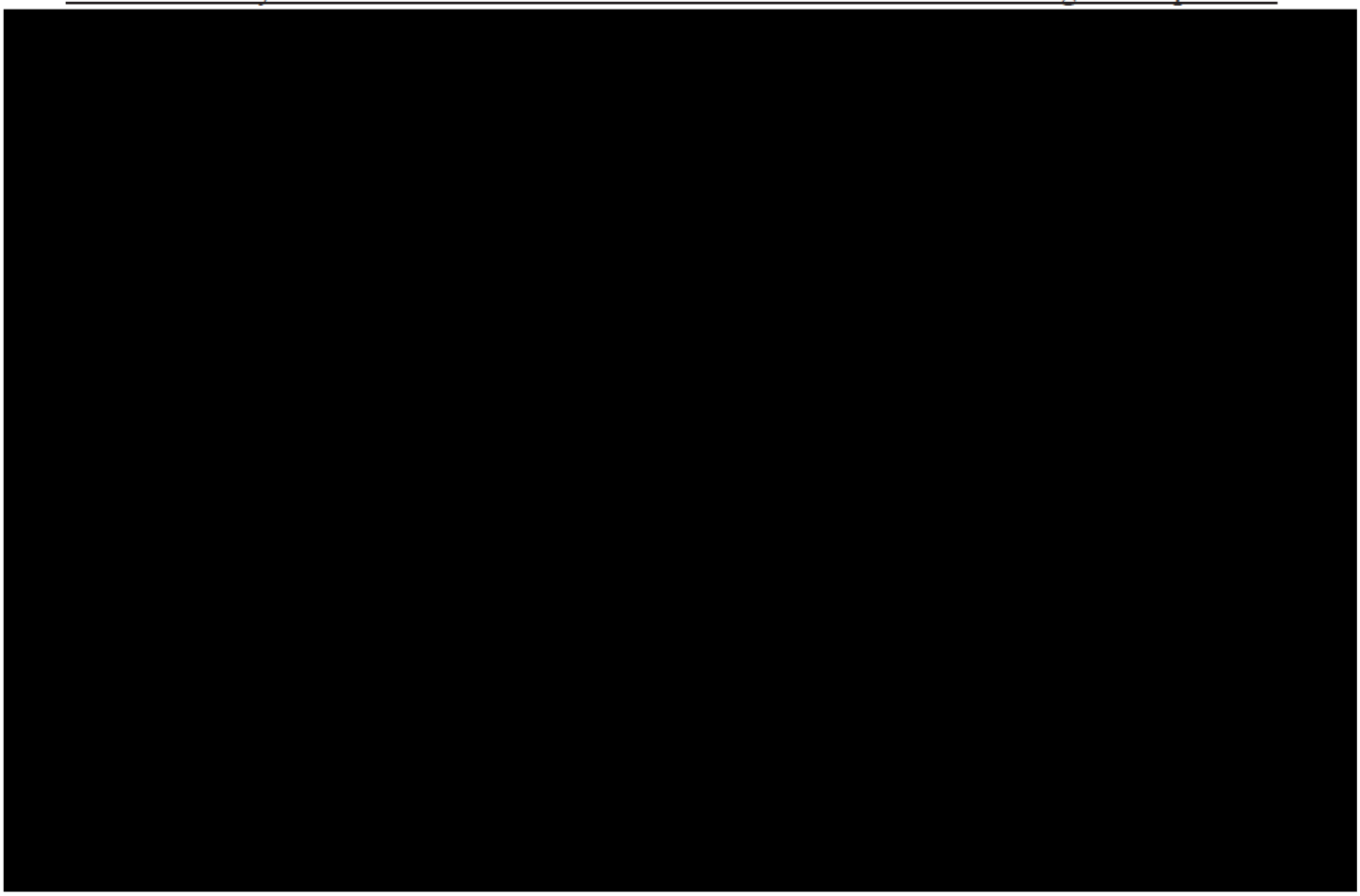
This SAP will be finalized and signed prior to the clinical database lock at the end of the dose escalation phase. All statistical analyses detailed in this SAP will be conducted using SAS® Version 9.2 or higher.

3. STUDY OBJECTIVES AND ENDPOINTS

The study objectives and endpoints for the dose escalation phase and the dose expansion phase are listed in Table 2. The analysis for the dose expansion objectives and endpoints will not be conducted and is not included in this SAP.

Table 2: Objectives and Endpoints

	Objectives	Endpoints	Phase of Analysis
Primary	Determine the safety of single agent CC-122 in subjects with R/R CLL/SLL.	Incidence and severity of adverse events using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) criteria (version 4.03), including Dose-Limiting Toxicities (DLTs).	Dose escalation
	Determine the safety and tolerability of the combination of CC-122 and ibrutinib and determine the RP2D of the combination in ibrutinib-naïve CLL/SLL subjects.	CC-122 in combination with ibrutinib: Determination of the NTD and MTD.	Dose escalation and safety and refinement of the RP2D in the dose expansion*.
	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.	CC-122 in combination with obinutuzumab: Determination of the NTD and MTD.	Dose escalation and safety and refinement of the RP2D in the dose expansion*.
Secondary	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.	CC-122 plasma concentrations when administered alone or in combination with ibrutinib, or obinutuzumab. CC-122 PK parameters when administered in combination with ibrutinib**	Dose escalation and dose expansion*
	Determine ibrutinib concentrations when given alone or in combination with CC-122	Ibrutinib plasma concentrations and/or PK parameters when administered in combination with CC-122.**	Dose escalation and dose expansion*
	Determine the preliminary efficacy of single agent CC-122, the combination of CC-122 and ibrutinib, and the combination of CC-122 and obinutuzumab.	Rates for 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)	Dose escalation and dose expansion*
		Minimal Residual Disease (MRD) negativity rate in bone marrow and peripheral blood.	Dose escalation and dose expansion*
		Duration of response (DoR).	Dose escalation and dose expansion*
		Progression-Free Survival (PFS).	Dose escalation and dose expansion*



4. INVESTIGATIONAL PLAN

4.1. Study Design and Plan

CC-122-CLL-001 is a Phase 1/2 multicenter, open-label, dose finding study to determine the safety 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-doses 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 3 to 6 subjects will be evaluated in each fixed-doses 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.

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-doses cohorts, the SRC will make the recommendation of whether to open the next dose cohort and the incremental increase in dose (i.e., 0.5 or 1.0 mg) after review of the safety data of the current dose cohort (after full enrolment 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-doses 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.

The same rules governing dose escalations in Arm A (see below) will be applied for intrasubject dose escalation cohorts in the combination arms.

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 progressive disease (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).

4.1.1. Dose Escalation Phase:

As of 05 Jul 2018, enrollment of new subjects into Phase 1 has been discontinued (per protocol amendment 7).

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-doses 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. (Previous protocol has starting CC-122 dose as 0.25 mg and 0.5 mg).

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 (i.e., 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 Protocol Section 8.2.8).

However, dose escalation per cycle is not mandatory if the subject is benefiting (i.e., 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 (i.e., 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 (i.e., < 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 Institutional Review Board (IRB) and/or Ethics Committee (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 PD, 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 mg and 1.0 mg fixed-doses 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 that 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 enrolment and completion of the DLT evaluation period).

CC-122 will be initiated on Cycle 2, Day 1 and administrated on a 5/7-day schedule. Ibrutinib 420 mg daily dose (QD) will be administered starting on Cycle 1, Day 1 (see Protocol 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 PD, 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 (see Section 17.2.2 for CC-122 Cycle definition).

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 $\leq$ 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 enrolment 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 Protocol 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 PD, 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% (e.g., >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-Doses Cohorts in Arms B and C:

An initial 3 subjects will be enrolled to each of the fixed-doses 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 Protocol Section 8.2.1).

After full enrolment 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 enrolment 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 less than 2 subjects have experienced a DLT at that dose level.

An intermediate dose (i.e. one between the NTD and the last dose level before the NTD) or additional subjects within any dose cohort may be required 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 greater than 20% of subjects experience a late toxicity necessitating dose reduction or discontinuation that is clearly not related to PD, 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.

4.1.2. Expansion Phase:

As of Protocol Amendment 7, Phase 2 Expansion Phase will not proceed.

4.1.3. Follow-up Phase:

The Follow-up Phase will begin at study treatment discontinuation. Subjects will have a visit at the End of Treatment (EoT) as soon as possible once Investigational Product (IP) has been discontinued and at 28 days

after the last dose of IP. All subjects discontinued for any reason other than PD, 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 PD, starts a new anti-CLL therapy, withdraws consent for further follow-up, or expires.

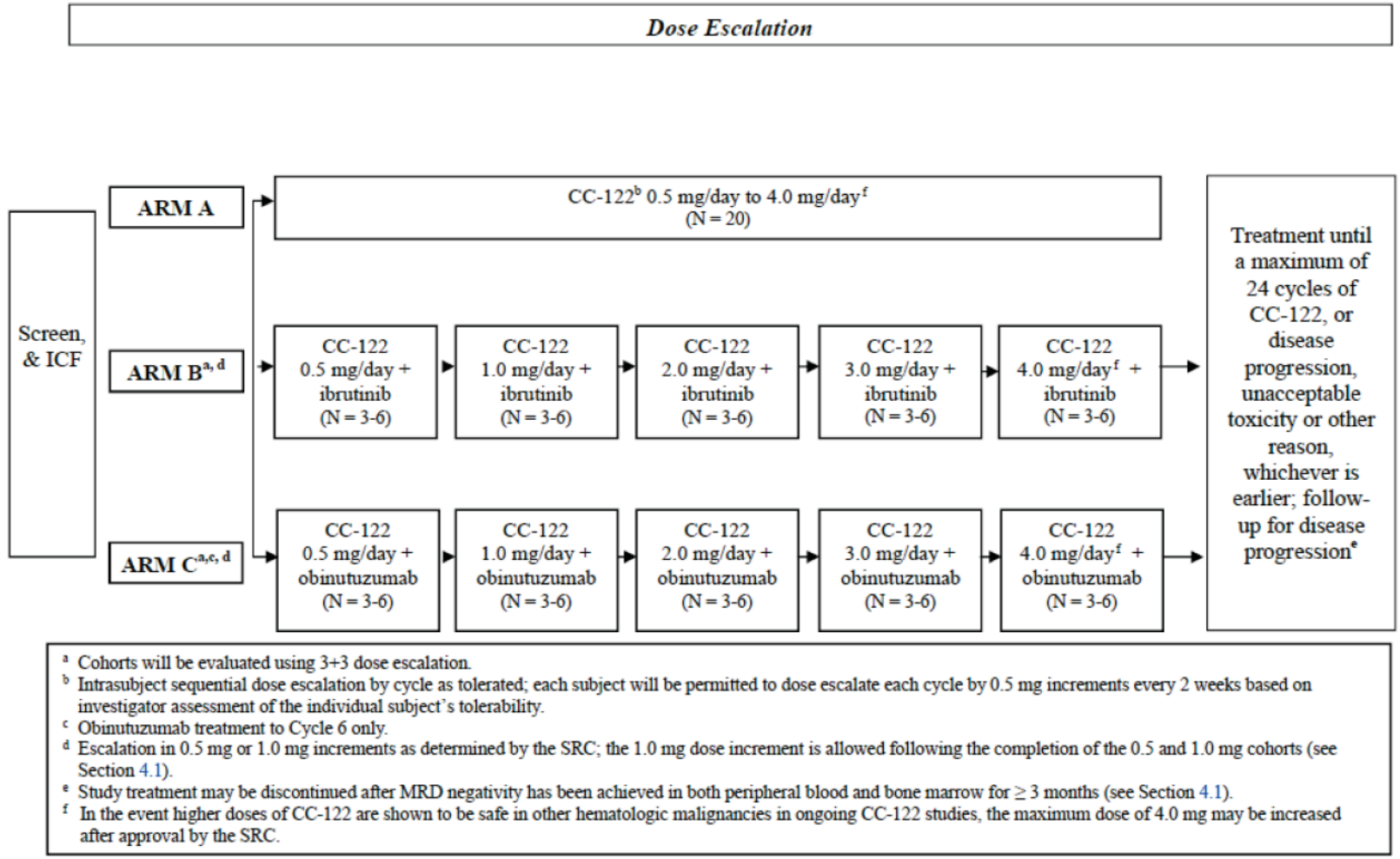
Efficacy assessments (including clinical examination, laboratory test, and Computerized Tomography (CT) scans as indicated in the tables of scheduled events) will continue until documented PD or initiation of subsequent anti-CLL therapy.

4.2. Study Treatments

The overall study design is presented in Figure 1.

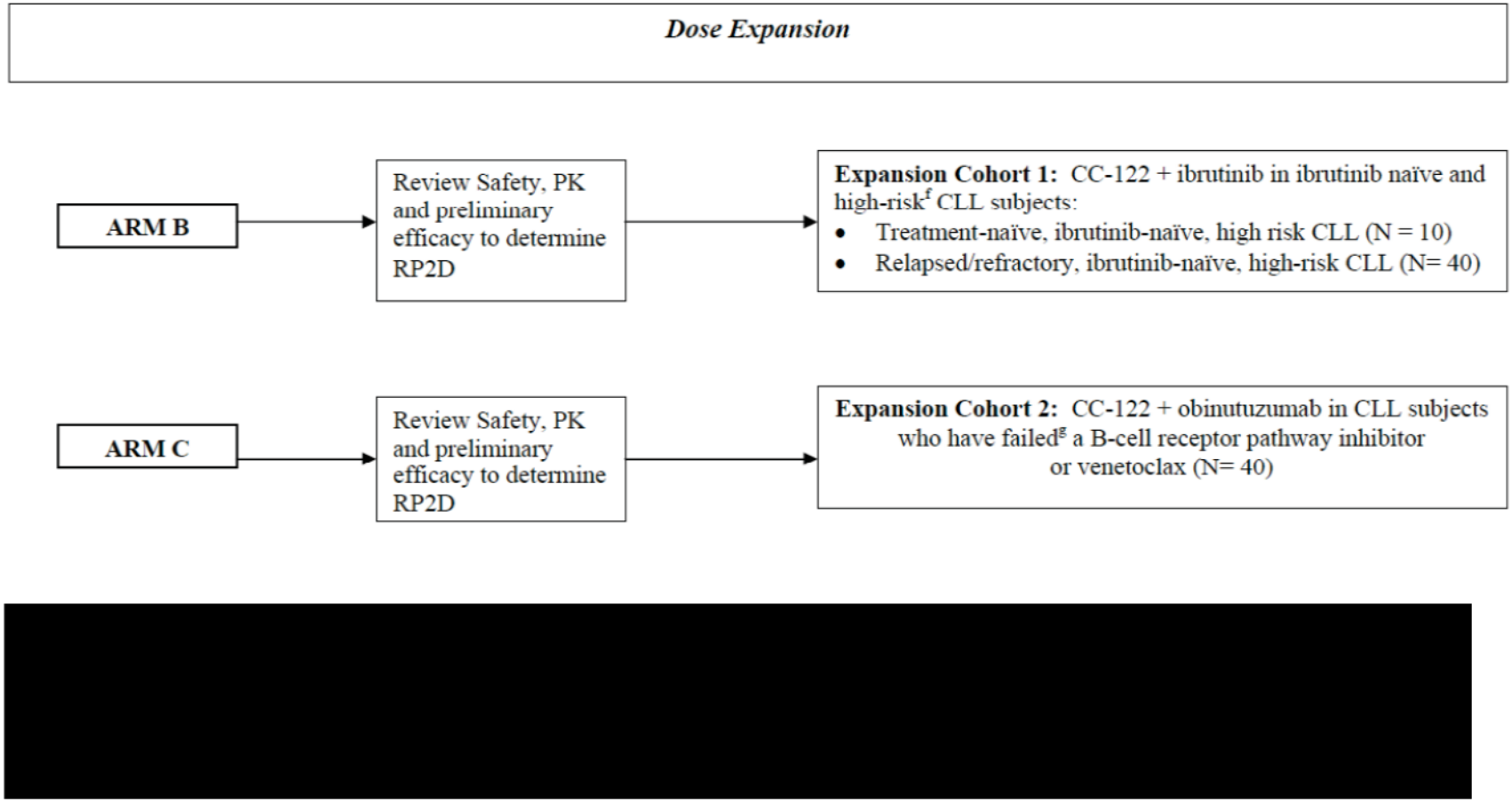
Per Protocol Amendment 7, Phase 2 Dose Expansion Phase will not proceed.

Figure 1: Overall Study Design



[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 1: Overall Study Design (continued)



Arm A (Single agent CC-122):

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 up to a maximum of 24 cycles of each cycle with intrasubject dose escalation permitted up to a maximum dose of 4.0 mg until PD, unacceptable toxicity or discontinuation for any other reason. 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. Subjects 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. Each cycle consists of 28 days.

Subjects who are enrolled to fixed dose cohorts (0.25 mg or 0.5 mg daily) in Arm A under earlier protocol amendments (i.e., protocol amendment 3 or 4) will be allowed to undertake intrasubject dose escalations as described above. Those subjects will switch to a 5/7 schedule as soon as the protocol amendment 5 has been approved at their site.

Arm B (CC-122 + ibrutinib):

Subjects in Arm B will be administered CC-122 orally on a 5/7-day schedule starting on Cycle 2 Day 1. CC-122 will be initiated until PD, unacceptable toxicity or discontinuation for any reason.

Subjects will take orally three 140 mg capsules of ibrutinib daily for a total dose of 420 mg. Ibrutinib will be administered daily starting Cycle 1 Day 1 up to a maximum of 24 cycles of CC-122 until PD, unacceptable toxicity or discontinuation for any other reason. For subjects who discontinue CC-122 prior to 24 cycles or if subjects 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 subjects to be switched to commercially available ibrutinib and/or other therapies at the discretion of the treating physician.

Arm C (CC-122 + 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 until PD, unacceptable toxicity or discontinuation for any other reason.

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. 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 subjects 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 subjects to be switched to commercially available therapies at the discretion of the treating physician.

Please refer to Protocol Section 8 for detailed description of study treatment.

4.3. Stratification and Randomization

This study is an open-label study. Treatment assignment does not require randomization, blinding, or stratification.

4.4. Sample Size Determination

During the Dose Escalation Phase of the study, an intrasubject does 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.

5. GENERAL STATISTICAL CONSIDERATIONS

5.1. Reporting Conventions

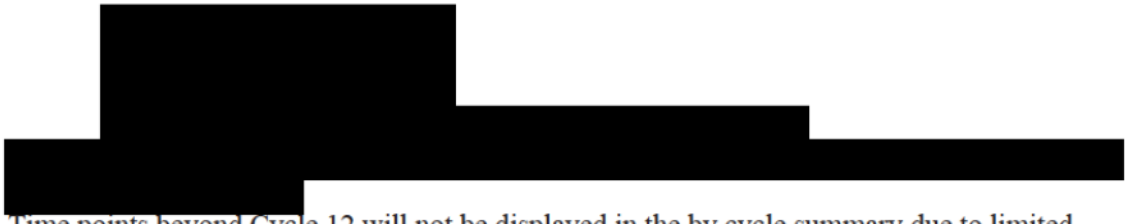
General reporting conventions for this study are:

- By default, descriptive statistics in this template include n (the corresponding sample size), Mean, Median, Standard Deviation (StdDev), Minimum (Min), and Maximum (Max). For selected outputs, first quartile (Q1) and third quartile (Q3) will also be displayed. Unless specified in the actual table shells, the mean, median, Q1, Q3 and the upper and lower limits of a two-sided 95% CI should be displayed to one more decimal place than the original data (derived analysis data). Standard deviation and standard error (SE) should be formatted to two decimal places more than the measured value. The minimum and maximum should be displayed to the same number of decimal places as the original data.
- P-values will be presented with 4 decimal places and presented in the format of "0.xxxx" or "<0.0001" or" >0.9999".
- Summary tables, listings, and any supportive SAS output will include a header of explanatory notes that will indicate the name of the sponsor, protocol number, data cut-off date and the page n of N.
- Summary tables, listings, and any supportive SAS output will include a footer of explanatory notes that will indicate, at a minimum, the following:
- Program source (e.g., SAS program name, including the path, that generates the output),
- Data extraction date (e.g., the database lock date, run date). The purpose of showing the data extraction date is to link the output to a final database, either active or archived, that is write-protected for replication and future reference.
- Output date (appearing on each output page). The output date will indicate the date the output was generated by the analysis program.
- Individual subject listings will display raw data collected in the clinical database and some key derived data used in the analyses.

Other general conventions include:

- The analysis specified by this SAP will include all treatment arms, dose cohorts (different dose levels or regimen), unless otherwise specified. Tables and figures will be summarized by treatment arm, dose cohorts and overall, if applicable.
- IP, study treatment and study drug are used interchangeably and, if not otherwise specified, are defined as any study-related treatment, including CC-122, ibrutinib, or obinutuzumab.
- First dose date of IP corresponds to the earliest date any dose (of CC-122, ibrutinib, or obinutuzumab) has been initiated (i.e. a non-zero dose was administered/infused).
- Last dose date of IP corresponds to the latest date any dose (of CC-122, ibrutinib, or obinutuzumab) has been administered/infused.

[redacted]



Time points beyond Cycle 12 will not be displayed in the by cycle summary due to limited sample size and the allowed flexible frequency of the test/measurement. Data from all time points will be included to evaluate the "most extreme" post-baseline value.

- For subjects in Arm A who have disease progress (PD) and then are treated with Ibrutinib or Obinutuzumab, following conversions will be applied:
  - In the database, the cycles after PD/arm switch will be labeled with suffix "-PD" and started from "Cycle 1 Day 1". For summary and reporting purpose, those visits will be mapped to the cycle numbers based on their original treatment schedule. For example, if a subject switch to Arm B (CC-122 plus Ibrutinib) after Cycle 2, the next visit labeled as "Cycle 1 Day 1 - PD" will be mapped as "Cycle 3 Day 1" and summarized accordingly.
  - Efficacy data collected up to the PD/arm switch, and all safety data collected in the study will be included in the summary under Arm A (and the starting dose level of CC-122 they initially received).
  - For study treatment and exposure summaries, the data collected before the treatment switch will be summarized under "CC-122 xx mg" according to the subject's initial CC-122 dose, the data collected after the treatment switch will be summarized under "CC-122 + Ibrutinib", or "CC-122 + Obinutuzumab", according to which drug the subject received.
  - Subjects who switch the treatment can report AEs which are
    - related to Ibrutinib or Obinutuzumab,
    - leading to discontinuation/reduction/interruption of Ibrutinib or Obinutuzumab.

    Those TEAEs will be summarized under Arm A (and starting dose of CC-122 they initially received).
- For subjects in Arm C who are not treated with CC-122:

  In the analysis based on Safety population, "Obinutuzumab Only" group will be used to summarize these subjects in Arm C who discontinue treatment/study without treatment of CC-122. In addition, "Arm C Total CC-122" and "Arm C Overall" group will be used to summarize the subtotal results without and with these subjects, respectively. In listings which are related with study drug and safety evaluations, "Arm/CC-122 dose" column will be displayed as "Arm C/0.0 mg" for these subjects.

5.2. Analysis Populations

All enrolled subjects will be used to assess subject disposition.

The demographic and baseline characteristics tables will use all populations defined in this section.

Drug exposure and all safety analyses (except for PK) will be based on the Safety population.

All DLTs will be based on the Dose Limiting Toxicity Evaluable population.

Efficacy analyses including Eastern Cooperative Oncology Group (ECOG) performance status (except for PK) will be based on the Safety population. Key Efficacy analyses [summary of ORR, DoR and PFS] will be based on both the Safety population and the Efficacy Evaluable (EE) population.

PK analyses will be based on the PK population.

All listings will use all enrolled subjects.

5.2.1. Safety Population

Safety population – all subjects who take at least one dose of any IP. Subjects will be summarized under the treatment arm and starting dose of CC-122 they initially received.

5.2.2. Dose Limiting Toxicity (DLT) Evaluable Population

DLT Evaluable population –

- Arm A: is defined as 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: is defined as 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: is defined as 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.

Subjects will be summarized under the starting treatment arm and starting dose of CC-122 they initially received.

5.2.3. Efficacy Evaluable (EE) Population

EE population – all subjects who completed at least one cycle (CC-122) of their assigned treatment regimen and have a baseline and at least one post-baseline efficacy assessment. Subjects will be summarized under the treatment arm they were enrolled.

5.2.4. Pharmacokinetic (PK) Population

PK population - all subjects who have at least one measurable CC-122 and/or ibrutinib concentration datum. Subjects will be summarized under the actual dose level corresponding to the PK sample collection.

Intensive PK Population is defined as all subjects who have at least one measurable CC-122 concentration datum from intensive sampling. Intensive PK population will be used to support summaries for CC-122 PK concentrations and parameters from the intensive sampling.

6. SUBJECT DISPOSITION

The total number of subjects who are considered screen failures will be summarized.

A summary of subject disposition will be presented by treatment arm, and dose cohort.

A tabulated summary of all analysis populations in Section 0 will be presented together with the subject disposition. A summary of Safety population subjects by site, treatment arm, dose cohort, and overall will be presented.

Reasons for discontinuation from the IP (CC-122, ibrutinib and obinutuzumab) will be summarized by treatment arm, dose cohort, and overall with the following categories:

- Progressive disease
- Adverse event
- Death
- Pregnancy
- Lack of efficacy
- Withdrawal by Subject
- Non-compliance with study drug
- Lost to follow up
- Study terminated by sponsor
- Transition to commercially available treatment
- Physician decision
- Disease relapse
- Symptomatic deterioration
- 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 *
- Other

Note the three reasons marked with "*" are allowed for treatment discontinuation in Protocol Amendment 7 and will be derived using corresponding standard wordings from the text field for "Other" specified reason: 'Start of new anti-CLL therapy', 'Maximum number of CC-122 cycles completed', 'CC-122 discontinued, additional 3 cycles of ibrutinib completed'.

Reasons for discontinuation from the study will be summarized by, treatment arm, dose cohort, and overall with the following categories:

- Death

- Adverse event
- Pregnancy
- Progressive disease
- Lack of efficacy
- Withdrawal by Subject
- Non- compliance with study drug
- Lost to follow up
- Study terminated by sponsor
- Transition to commercially available treatment
- Physician decision
- Disease relapse
- Symptomatic deterioration
- 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 *
- Other

Similarly, the three reasons marked with "*" are allowed for study discontinuation in Protocol Amendment 7 and will be derived using corresponding standard wordings from the text field for "Other" specified reason: 'Start of new anti-CLL therapy', 'Maximum number of CC-122 cycles completed', 'CC-122 discontinued, additional 3 cycles of ibrutinib completed'.

Protocol violations (PV) and protocol deviations (PD) will be identified and assessed by the clinical research physician or designee following company standard operational procedure. Protocol deviations and violations will be summarized by category and sub-category for the Safety population.

The following by-subject listing of subjects with demographic information included will be provided:

- Subject listing of discontinuation for any reason.
- Subject listing of screen failures.
- Subject listing of protocol violations and protocol deviations with an additional column to flag the protocol deviations that are identified as protocol violations.

7. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographics and baseline characteristics will be summarized by treatment arm, dose cohort, and overall for all populations defined in Section 0, if not otherwise specified. Individual subject listings for the all enrolled subjects will be provided to support the summary tables.

7.1. Demographics

The continuous demographic variables, age (year), weight (kg), height (cm), Body Mass Index (BMI) (kg/m^2) and Body Surface Area (BSA) (m^2) will be summarized using descriptive statistics (e.g. n, mean, standard deviation, median, minimum, and maximum) by treatment arm, dose cohort and overall. BMI category (<25 kg/m^2, ≥25 kg/m^2, Missing) will be summarized with frequency counts.

Age is calculated based on the date of birth and the date of informed consent. In the case date of birth is missing or partial, age collected in the Case Report Form (CRF) will be used. Age category (≤70, >70) will be summarized with frequency counts.

BSA (m^2) is calculated as follows:

$$\left(\frac{Height\ (cm) \times Weight\ (kg)}{3600}\right)^{1/2}$$ (based on the Mosteller formula).

BMI is calculated as follows:

$$\left(\frac{Weight\ (kg)}{(Height\ (m))^2}\right)$$

Race, sex and ethnicity will be summarized with frequency tabulations by treatment arm, dose cohort and overall.

7.2. Baseline Characteristics

Baseline clinical characteristics include temperature (°C), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), pulse rate (beats per minute [bpm]), respiration rate (breaths per minute [BPM]), overall interpretation of Electrocardiogram (ECG), ECOG performance status (0, 1 or >1), B-symptoms, disease diagnosis (CLL or SLL), current stage/prognostic classification and Minimal Residual Disease (MRD) (provided from eCRF).

The Cumulative Illness Rating Scale (CIRS) score will be documented by a qualified clinician at the time of the screening visit. The CIRS score will be collected to assess the performance status and fitness of subjects. Baseline CIRS will be presented as below:

- The total score category: 0, 1-3, 4-6, 7-9, 10-11, > 11;
- At least one grade 3 or higher comorbidities: Yes, No.

[redacted]

Baseline best corrected visual acuity, slit lamp examination results and ophthalmologic examination results will be summarized in an additional table for Safety population only.

For Safety population only, summary statistics will be provided for baseline Left Ventricular Ejection Fraction (LVEF), overall interpretation of LVEF, laboratory data (Hemoglobin [HGB]*, Potassium*, Total Bilirubin*, Aspartate Aminotransferase* [Aspartate Transaminase (AST) or serum glutamic oxaloacetic

transaminase (SGOT)], Alanine Aminotransferase* [Alanine Transaminase (ALT) or serum glutamate pyruvic transaminase (SGPT)], Lactate Dehydrogenase [LDH] , Uric Acid, Troponin-T, C-Reactive Protein, Direct Antiglobulin test, White Blood Cell (WBC) count*, ALC*, Absolute Neutrophil Count (ANC)*, Calcium*, Phosphorous, Serum Creatinine, Alkaline Phosphatase [ALP]*) and Creatinine Clearance. Frequency counts for NCI-CTCAE grades will be also provided for the laboratory tests above with asterisk sign (*).

Categorical baseline variables will be summarized using frequency counts and percentage by treatment arm, dose cohort and overall. Continuous baseline variables will be summarized by descriptive statistics in the same way as continuous demographic variables (e.g., n, mean, standard deviation, median, minimum, and maximum). Listings will be presented for all enrolled subjects.

7.3. Medical History

Medical history will be summarized by frequency counts and percentage for the Safety population. The summary will be tabulated by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Affairs® (MedDRA) Version 22.0 or higher and presented by treatment arm, dose cohort and overall. Listings will be presented for all enrolled subjects.

7.4. Prior Therapies

The number of prior therapies for CLL/SLL collected in the CRF will be summarized for prior radiation therapies, prior systemic anti-cancer therapies and prior stem cell transplants separately by frequency tabulations for each treatment arm, dose cohort and overall for the Safety population. The therapies with the same sequence/regimen number are counted as one prior therapy. Listings will also be presented by treatment arm and dose cohort for all enrolled subjects.

Novel agent failure, information collected for resistance/intolerance of BTK inhibitor, PI3K inhibitor and Venetoclax, will be listed by treatment arm and dose cohort for all enrolled subjects.

8. STUDY TREATMENTS AND EXTENT OF EXPOSURE

Study treatment and extent of exposure summaries will be provided based on the Safety population. Descriptive statistics will be provided for treatment duration, number of cycles, cumulative dose, actual dose intensity and relative dose intensity by treatment arm, dose cohort and overall. Relative dose intensity is used in place of the treatment compliance. The distribution of treatment duration and number of cycles will be analyzed by frequency counts on different intervals of treatment duration and number of cycles.

For subjects in Arm A who switch treatment, the convention outlined in Section 5.1 will be applied. A by-subject listing will be provided for the subjects who received progressive disease subsequent treatment in Arm A.

8.1. Treatment Duration

Treatment duration is presented in days or weeks as appropriate. For each treatment arm the treatment duration is:

Arm A:

Treatment duration (days) = [(Last non-missing dose date of CC-122) - (First non-missing dose date of CC-122) + 1], where the first non-missing dose date of CC-122 is Cycle 1 Day 1.

Arm B:

CC-122 treatment duration (days) = [(Last non-missing dose date of CC-122) - (First non-missing dose date of CC-122) + 1], where the first non-missing dose date of CC-122 is Cycle 2 Day 1;

Ibrutinib treatment duration (days) = [(Last non-missing dose date of ibrutinib) - (First non-missing dose date of ibrutinib) + 1].

Arm C:

CC-122 treatment duration (days) = [(Last non-missing dose date of CC-122) - (First non-missing dose date of CC-122) + 1], where the first non-missing dose date of CC-122 is Cycle 1 Day 9;

Obinutuzumab treatment duration (days) = Minimal (28 days × number of cycles of non-zero/non-missing Obinutuzumab dose, End of study date – First dose date of any IP +1.

8.2. Cumulative Dose and Dose Intensity

The cumulative actual dose and actual dose intensity for each study drug (CC-122, ibrutinib, obinutuzumab) will be presented by dose cohort for each arm. The actual dose intensity is defined as the cumulative actual dose divided by the total length of treatment for the IP.

CC-122:

The cumulative actual dose of CC-122 is defined as the sum of all doses of CC-122 taken across the treatment period.

The cumulative expected dose of CC-122 is calculated as below:

- For the cycles on daily schedule of CC-122 (only applicable to Arm A subjects):

  Expected dose = (stop date - start date of CC-122 administration +1) × planned daily dose;

- For the cycles on 5/7 days schedule of CC-122:

$Expected\ dose = Planned\ daily\ dose \times [\lfloor \frac{Dur}{7} \rfloor \times 5 + \min(5, Dur - \lfloor \frac{Dur}{7} \rfloor \times 7)]$, where Dur is the treatment duration for CC-122.

Repeat this derivation for each planned dose (i.e. take into account the dose escalation but not the decrease due to AE) and sum up.

The Expected dose intensity for CC-122 is the cumulative expected dose divided by the total length of treatment duration for CC-122.

Ibrutinib (Arm B)

The cumulative actual dose of ibrutinib is the sum of all doses of Ibrutinib taken across the treatment period. The cumulative expected dose of ibrutinib is the (planned daily dose × Ibrutinib treatment duration in days). The expected dose intensity for Ibrutinib is the planned daily dose – 420 mg/day.

Obinutuzumab (Arm C):

The cumulative actual dose of obinutuzumab is the sum of all doses of obinutuzumab taken across the treatment period. The cumulative expected dose of obinutuzumab is the sum of the planned dose per Table 10 in the protocol Section 8.2.2.3 based on the last visit which has been completed:

Last visit completed	Cycle 1 Day 1	Cycle 1 Day 2	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 2 Day 1	Cycle 3 Day 1	Cycle 4 Day 1	Cycle 5 Day 1	Cycle 6 Day 1
Cumulative expected dose (mg)	100	1000	2000	3000	4000	5000	6000	7000	8000

The Expected dose intensity for obinutuzumab is the cumulative expected dose divided by the total length of treatment duration for obinutuzumab.

8.3. Relative Dose Intensity

Relative dose intensity is used in place of the treatment compliance. Relative dose intensity is defined as actual dose intensity divided by expected dose intensity.

Additionally, the number and percentage of subjects will be summarized by ≤80% and >80% for relative total dose intensity of CC-122, for CC-122 and ibrutinib in Arm B, for CC-122 and obinutuzumab in Arm C, the actual category can be data driven.

8.4. Dose Reduction/Interruptions

Dose reduction is defined as a decrease in dose (non-zero) relative to the immediately previous dose (or assigned dose if the first dose). Dose interruption occurs if the record of actual administered dose is zero except as required by the protocol (i.e. for CC-122 the 2 out of 7 days when the subject does not receive CC-122 drug). If an interruption happens at the start of a cycle and causes the cycle to be postponed, it is also called dose delay. Consecutive zeros are counted as one interruption. The reductions will be derived from the data collected.

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 reductions are allowed for obinutuzumab, but treatment may be discontinued at the discretion of the investigator for severe infusion or allergic reactions.

Dose reduction, where applicable, and interruption will be summarized separately by dose cohort and overall for each arm. Summaries include the following:

- Number of subjects with dose reductions or interruptions;
- Number of dose reductions/interruptions due to AE;
- Descriptive statistics of time to the first dose reduction or interruption (from the first dose) due to an AE for those who have at least one dose reduction or interruption due to an AE;
- Descriptive statistics of total days of dose reduction or interruption due to an AE for those who have at least one dose reduction or interruption of CC-122 and Ibrutinib due to an AE;
- Number and percentage of subjects who have at least two dose reductions or interruptions.

9. PRIOR/CONCOMITANT MEDICATIONS AND PROCEDURES

Medications initiated prior to the start of first dose of IP (i.e. any study drug) and are continued after the first dose of IP will be counted as both prior and concomitant medications.

Summary tables of prior and concomitant medications and prior and concomitant procedures will be provided for the Safety population. Listings will also be provided for all enrolled subjects.

The Anatomical Therapeutic Chemical (ATC) coding scheme of the World Health Organization (WHO) Drug Dictionary (WHODrug) will be used to group medications into relevant categories for these tabulations. Individual listings of prior and concomitant medications/procedures will be provided to support the tables.

9.1. Prior Medications

Prior medications are defined as medications that were started before the first dose of the study drug and either ended before the start of the study treatment or continued after initiation of study treatment. Prior medications will be summarized in frequency tabulations by dose cohort and overall for each treatment arm and by ATC level 2 category and preferred drug name.

9.2. Concomitant Medications

Concomitant medications are defined as non-study medications that were either initiated before first dose of any study drug and continued during the study treatment or initiated during the study treatment exposure period, defined as the interval between the date of first administration of any study treatment and the last dose of any study treatment plus 28 days. Concomitant medications will be summarized in frequency tabulations by treatment arm, dose cohort and overall and by ATC level 2 category and preferred drug name.

In addition, the number of subjects with concomitant growth factor will be summarized in frequency tabulations by treatment arm, dose cohort and overall and by ATC level 2 category and preferred drug name.

9.3. Concomitant Procedures and Surgeries

Concomitant procedures/surgeries will be summarized by SOC and PT coded with the MedDRA dictionary Version 22.0 or higher using frequency tabulations by treatment arm, dose cohort and overall. Concomitant procedures/surgeries are defined as procedures/surgeries that were performed during the study treatment exposure period, defined as the interval between the date of first administration of any study treatment and the last dose of any study treatment plus 28 days. Concomitant procedures/surgeries will be listed.

[redacted]

10. EFFICACY ANALYSIS

The efficacy endpoints of this study include ORR, MRD, DoR and PFS based on the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) [redacted] with modifications [redacted] for subjects with CLL and based on the revised International Workshop Lymphoma criteria for response assessment [redacted] for subjects with SLL. For subjects with CLL see Table 3 for details and for subjects with SLL see Table 4 for details. 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 every three cycles during the first two years and every 6 cycles thereafter at the time of physical examinations until documented progression or initiation of subsequent CLL therapy. PD based on physical and/or laboratory tests at any time should be confirmed by CT scan. CR/CRi confirmation by bone marrow examination must be completed within 12 weeks after clinical criteria have been met. Furthermore, CT scans at Screening, end of Cycle 6 are mandatory (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).

Tables and listings will be provided to describe the efficacy endpoints tabulated by dose cohort and overall for each treatment arm. Efficacy analysis will include a summary of ORR, MRD, DoR and PFS.

For each subject the survival status will be provided in a listing.

In addition, a waterfall of the best percentage change from baseline sum of the product of the perpendicular diameters for multiple lesions will be provided for subjects with measurable nodal lesions at baseline. Each subject's best percent change will be represented by a bar, with a pattern specific to the dose level to which they were initially assigned to (in dose escalation phase).

10.1. Objective Response Rate (ORR) and Minimal Residual Disease (MRD)

For subjects treated with CC-122 and CC-122 in combination with ibrutinib or obinutuzumab, investigators will use the updated IWCLL guidelines for diagnosis and treatment of CLL [redacted] with modifications [redacted] for subjects with CLL and the revised International Workshop Lymphoma criteria for response assessment [redacted] for subjects with SLL.

Table 3: Response Definition after Treatment for Chronic Lymphocytic Leukemia Subjects

	Parameter	Complete Response*	Partial Response*	Partial Response with Lymphocytosis*	Progressive Disease***
Group A	Lymphadenopathy	None > 1.5 cm	Decrease ≥ 50% from the baseline in the SPD of the index nodal lesions	Decrease ≥ 50% from the baseline in the SPD of the index nodal lesions	Increase from the nadir by ≥ 50% in the SPD of lesions or new lesion**
	Hepatomegaly	None	Decrease in the enlargement of the liver by ≥ 50% (minimum 2 cm decrease) from baseline or LVD decrease to ≤ 18 cm by imaging	Decrease in the enlargement of the liver by ≥ 50% (minimum 2 cm decrease) from baseline or LVD decrease to ≤ 18 cm by imaging	Increase ≥ 50% in the enlargement of the liver from nadir (with a minimum 2 cm increase and a minimum LVD of 20 cm) or new lesion**
	Splenomegaly	None	Decrease in the enlargement of spleen by ≥ 50% (minimum 2 cm decrease) from baseline or LVD decrease to ≤ 12 cm by imaging.	Decrease in the enlargement of spleen by ≥ 50% (minimum 2 cm decrease) from baseline, or LVD decrease to ≤ 12 cm by imaging.	Increase ≥ 50% in splenic enlargement from nadir (with a minimum 2 cm increase and a minimum LVD of 14 cm) or new lesion**
	Blood Lymphocytes	< 4000/μL	Decrease ≥ 50% from baseline	Persistent lymphocytosis due to mechanism of action of IP	Increase ≥ 50% over nadir (with at least ALC of 5000/ μL)
	Marrow	Normocellular, < 30% lymphocytes, no B-lymphoid nodules Hypocellular marrow defines Cri	50% reduction in marrow infiltrate, or B-lymphoid nodules	50% reduction in marrow infiltrate, or B-lymphoid nodules	-

Table 3: Response Definition after Treatment for Chronic Lymphocytic Leukemia Subjects (Continued)

	Parameter	Complete Response*	Partial Response*	Partial Response with Lymphocytosis*	Progressive Disease***
Group B	Platelet count	> 100,000/μL	> 100,000/μL or increase ≥50% over baseline	> 100,000/μL or increase ≥50% over baseline	Current platelet is < 100 x 10^9/L and there has been a decrease of ≥ 50% from baseline secondary to CLL
	Hemoglobin	> 11.0 g/dL	> 11.0 g/dL or increase ≥50% over baseline	> 11.0 g/dL or increase ≥50% over baseline	The current hemoglobin is < 11 g/dL and there has been a decrease of > 2g/dL from baseline secondary to CLL
	Neutrophils	> 1500/μL	> 1,500/μL or increase ≥ 50% over baseline	> 1,500/μL or increase ≥ 50% over baseline	-

Abbreviations: ALC = absolute lymphocyte count; CLL = chronic lymphocytic leukemia; CRi = complete response with incomplete marrow recovery; IP = investigational product; LD = longest diameter; LPD = longest perpendicular diameter; LVD = longest vertical dimension; SPD = sum of the product of the perpendicular diameters for multiple lesions.

Notes:

* Complete Response (CR): all of the criteria have to be met, and subjects have to lack disease-related constitutional symptoms; Partial Response (PR) and Partial Response with Lymphocytosis (PRL): at least two of the criteria of Group A plus one of the criteria of Group B have to be met. There are two exceptions in which only 1 criterion is needed: 1) only lymphadenopathy is present at baseline (applicable to PR only); 2) only lymphadenopathy and lymphocytosis are present at baseline. In these two scenarios (applicable to PRL only), only lymphadenopathy must improve to the extent outlined in the Group A criteria in the table; Stable Disease (SD) is the absence of Progressive Disease (PD) and failure to achieve at least PR; PD: at least one of the above criteria of Group A or Group B has to be met. Lymphocytosis as a criterion for PD is not applicable to ibrutinib treated subjects and generally requires other supportive evidence of PD. Response or PD assessment of lymphadenopathy may also be based on longest diameters of the enlarged lymph nodes and the same method should be applied consistently to all lesions.

**New lesion is defined as any of the following: a new node that measures >1.5cm in the LD and >1.0 cm in the LPD; new or recurrent hepatomegaly ≥20 cm in LVD; new or recurrent splenomegaly ≥14 cm in LVD; unequivocal appearance or re-appearance of an extra-nodal lesion of any size; New non-index disease (ascites, pleural effusion, or other abnormalities) confirmed to be related to CLL progression.

***Additional criteria for PD include: 1) transformation to a more aggressive histology (e.g., Richter syndrome) as established by biopsy (the date of biopsy being the date of progression in the subject who has no earlier objectively documented CLL progression). 2) Unequivocal increase in size of non-index disease (e.g., effusions, ascites, or other organ abnormalities confirmed to be related to CLL).

[redacted]

Table 4: Summary of Revised Criteria for Response Assessment for Small Lymphocytic Lymphoma

Response Category	PET-CT-Based Response	CT-Based Response
CR	Complete metabolic response Score 1, 2, or 3 with or without a residual mass on 5PS A complete metabolic response even with a persistent mass is considered a complete remission	Target nodes/nodal masses must regress to ≤ 1.5 cm in longest diameter No extralymphatic sites of disease
PR	Partial metabolic response Score 4 or 5 with reduced uptake compared with baseline and residual masses of any size	All of the following: ≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites Spleen must have regressed by > 50% in length beyond normal
SD	No metabolic response Score 4 or 5 with no significant change in FDG uptake from baseline	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites No criteria for PD are met
PD	Progressive metabolic disease Score 4 or 5 with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma Bone marrow: New or recurrent FDG-avid foci	At least 1 of the following: An individual node/lesion must be abnormal with: Longest diameter > 1.5 cm and increase by ≥ 50% from nadir and An increase by longest diameter or shortest diameter from nadir In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline New or recurrent splenomegaly New or clear progression of pre-existing non-measured lesions Regrowth of previously resolved lesions Bone marrow: New or recurrent involvement

Abbreviations: 5PS: 5-point scale; CR=complete response; CT = computed tomography; FDG = fluorodeoxyglucose; PET = positron emission tomography; PR = partial response; PD = progressive disease; SPD = sum of the product of the perpendicular diameters for multiple lesions.
Definition: nadir = the smallest value from all previous lesion size assessments (not including the current assessment).
[redacted]

Peripheral blood for MRD assessment will be collected during screening, every 6 cycles (only if subjects is receiving CC-122, up to a maximum of 24 cycles), and at the time of Complete Response (CR) and/or Complete Response with incomplete marrow recovery (CRi) confirmation visit (within 12 weeks after clinical and laboratory response criteria have been met). For those subjects confirmed to be MRD positive in the peripheral blood at the CR/CRi confirmation visit, a peripheral blood sample for MRD assessment will be collected approximately every 6 cycles thereafter until MRD negativity is achieved or relapse/progression is documented.

Peripheral blood for MRD assessment will also be collected at the time of Partial Response (PR), including Partial Response with Lymphocytosis (PRL), within 12 weeks after clinical, imaging, and laboratory

response criteria have been met. 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.

Response will be assessed by the investigator using modified IWCLL guidelines for diagnosis and treatment of CLL for CLL subjects and the revised International Workshop Lymphoma criteria for response assessment for SLL subjects. 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, nodular Partial Response [nPR], PR, PRL, stable disease [SD], PD with histologic transformation [PDwH] and PD without histologic transformation [PDw/oH], not evaluable, not evaluable due to TFR and other) will be provided for each treatment arm and dose level.

ORR will be the proportion of subjects with (CR + CRi + PR + nPR + PRL [PRL is only applicable to Arm B]). ORR will be summarized by dose cohort and overall for each treatment arm for the Safety and the EE populations. The corresponding two-sided 95% CI will be calculated for CLL/SLL cohorts using Clopper-Pearson [redacted] method.

Response rate will also be presented for end of cycle 3, end of cycle 6 and end of cycle 12 assessments. As the length of cycles can be varied due to dose escalation, following rules will be applied to the summary:

- for the best response at the end of cycle 3, responses collected up to Day 85 will be used;
- for the best response at the end of cycle 6, responses collected up to Day 169 will be used; only subjects who have assessment beyond Cycle 3 (Day 85) are included in this summary;
- for the best response at the end of cycle 12, responses collected up to Day 337 will be used; only subjects who have assessment beyond Cycle 6 (Day 169) are included in this summary.

MRD negativity rate will be presented using frequency counts and percentages together with CIs for each treatment arm and dose level for the Safety and EE populations. The corresponding two-sided 95% CI will be calculated using Clopper-Pearson [redacted] method. The MRD negativity rate will be presented by source of sample collection (BM, PB, BM and/or PB).

10.2. Duration of Response (DoR)

For subjects with response as PR, nPR, PRL (applicable to Arm B only), CRi or CR, the Duration of Response (DoR) is measured from the time the response is first met until the first date that PD or death is documented. Subjects who neither progress nor die or who withdrew consent or are lost to follow-up prior to documentation of progression will be censored at the date of their last adequate response assessment. Adequate efficacy assessment encompasses protocol defined assessments of tumor lesions (lymph nodes, spleen, and liver), peripheral blood test, bone marrow assessment when indicated, and clinical assessment.

The Kaplan-Meier estimate of median DoR along with a two-sided 95% CI will be provided by dose cohort and overall for each treatment arm in a table using Safety and EE populations.

A listing of all subjects with their response and best overall response will be provided. A separate listing will also include the DoR (for subjects with response as CR, CRi, PR, nPR or PRL [PRL applicable to Arm B only], based on the criteria defined above for CLL and SLL).

10.3. Time to Response and Time to Best Overall Response

Time to Response

For subjects with response as PR, nPR, PRL (applicable to Arm B only), CRi or CR, the time to response is measured from the first dose date of any treatment to the date a response is first met (PR, nPR, PRL [applicable to Arm B only], CRi or CR). Subjects who did not have a response are not included in the analysis.

The median, mean, standard deviation, minimum and maximum of the time to response will be provided by dose cohort and overall for each treatment arm in a table using Safety and EE populations.

Time to Best Overall Response

For subjects with response as PR, nPR, PRL (applicable to Arm B only), CRi or CR, the time to best overall response is measured from the first dose date of any treatment to the date the best overall response is first met.

The best overall response is the best response amongst the following response: CR, CRi, nPR, PR and then PRL. Subjects who did not have a response are not included in the analysis.

The median, mean, standard deviation, minimum and maximum time to response will be provided by dose cohort and overall for each treatment arm in a table using Safety and EE populations.

A by-subject listing will be displayed for the time to response and time to best response for responder alongside the DoR.

10.4. Progression-Free Survival (PFS)

Progression-Free Survival (PFS) will be calculated as the time from first IP (i.e. any study drug) dose date to the first documented progression or death due to any cause during or after the treatment period, whichever occurs first. PD is determined by criteria defined in Table 3 for CLL and Table 4 for SLL.

A subject who has neither progressed nor died will be censored on the date of his or her last adequate tumor response assessment. Subjects without adequate baseline or post-baseline efficacy assessments will be censored on their first dose dates. Table 5 summarizes the different scenarios for consideration for censoring.

Table 5: Censoring Method for Progression-Free Survival Time

Situation	Date of Progression or Censoring	Situation Outcome
No post-baseline response assessments	Date of the treatment start	Censored
Progression documented before subsequent anti-CLL/SLL therapy	Earliest of sample collection date, target and non-target lesions date for samples supported the response assessment	Events
Death before first PD and subsequent anti-CLL/SLL therapy	Date of death	Events
No progression nor death	Date of last adequate response assessment with evidence of no progression	Censored
Study discontinuation for reasons other than PD or death	Date of last adequate response assessment with evidence of no progression	Censored

New anti-CLL/SLL treatment started with no claim of progression	Date of last adequate assessment with evidence of no progression prior to the start of new anti-CLL/SLL treatment	Censored

Analysis of PFS will be provided for different dose cohorts and overall by treatment arm in a table. Median and 1st quartile PFS will be estimated using Kaplan-Meier estimates and the 95% CI will be computed using the method of Klein and Moeschberger [redacted] with log-log transformation for each treatment arm and dose level. The number of events, subjects censored, and the Kaplan-Meier estimates of PFS rates at the time points of three, six months, one, two and three years along with the 95% CI of rate estimates, will also be provided. (For selecting timepoints: 1 month = 30 days, 1 year = 365 days.)

A listing of subjects who progressed based on the criteria defined above for CLL and SLL, and who died will be presented.

10.5. Bone Marrow Examination

Bone marrow aspirate is optional at screening and bone marrow aspirate and biopsy will be mandatorily 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). Listings for bone marrow aspirate and biopsy (all parameters collected) will be provided by dose cohort for each treatment arm for all enrolled subjects.

Bone marrow collected for MRD assessment (MRD -, MRD + and not done) will be listed for all enrolled subjects. Frequency counts and percentages will be provided for MRD negativity by dose cohort and overall for each treatment arm for the Safety and EE populations.

10.6. ECOG Performance Status

Shift table from baseline to best post-baseline in ECOG performance status will be displayed by dose cohort and overall by treatment arm for the Safety population. A listing of ECOG grade will be provided as well.

10.7. B-symptoms Evaluation

Assessment of the presence or absence of B-symptoms will be performed at screening and on Day 1 for all cycles, at EoT and 28 days post last dose of IP. After the first 12 cycles of CC-122, in the absence of adverse events related to CC-122, and as clinically indicated, some Day 1 clinic visits and assessments may become less frequent.

B-symptoms are defined as any one or more of the following disease-related symptoms or signs:

- Unintentional weight loss $\geq$ 10% within the previous six months.
- Significant fatigue (i.e., ECOG performance status of two or higher; cannot work or unable to perform usual activities).
- Fevers of greater than 100.5°F or 38.0°C for two or more weeks without other evidence of infection.
- Night sweats for more than one month without evidence of infection.

Summary tables for B-symptoms for weight loss, fatigue, fever and night sweats will be provided by visit, dose cohort and overall for each treatment arm using Safety population. Listing of B-symptoms will be provided to support the tables.

10.8. Physical Examination for Efficacy Analysis

Data collected from physical examination for measurable lymph node assessment, physical examination for non-measurable lymph node assessment will be listed.

11. SAFETY ANALYSIS

The purpose of this section is to define the safety parameters for the study and to summarize the safety results of the study. All summaries of safety data will be conducted using the Safety population and will be presented by treatment arm, dose cohort and overall. Safety measurements will include AEs, clinical laboratory information, vital sign measurements, cardiac laboratory assessment, 12-lead ECGs, LVEF assessments, monitoring for TLS and tumor flare, ophthalmological and pregnancy status evaluation. Individual subject listings (including coagulation tests such as Prothrombin Time, International Normalized Ratio (INR) and Partial Thromboplastin Time (PTT) assessment) will be provided to support the tables.

If an EoT measurement is conducted for those subjects who discontinue from the study, the data from the EoT visit will be included as a separate visit in the summary table. In addition, the data from the EoT visit as well as follow-up at 28 days visit will also be included in plots for parameters of individual subjects over time, unless otherwise specified.

11.1. Adverse Events

11.1.1. Summary of Adverse Events

AEs will be analyzed in terms of Treatment-Emergent Adverse Events (TEAEs) which are defined as any AEs that begin or worsen on or after the start of IP through 28 days after the last dose of IP. All AEs will be coded using the MedDRA® dictionary Version 22.0 or higher.

If a subject experiences the same AE more than once with a different toxicity grade, then the event with the highest grade will be tabulated in "by grade" tables. If a subject experiences multiple AEs under the same PT (SOC), then the subject will be counted only once for that PT (SOC). In addition, AEs with a missing intensity will be presented in the summary table as an intensity category of "Missing" and will not be imputed.

The incidence of TEAEs will be summarized by MedDRA SOC and PT. The intensity of AEs will be graded 1 to grade 5 by investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03 with the exception of tumor flare (NCI CTCAE version 3.0), tumor lysis [redacted] and laboratory abnormalities as recommended by the IWCLL guidelines for the diagnosis and treatment of chronic lymphocytic leukemia[redacted] For all other AEs, the intensity will be determined by the investigator as mild (Grade 1), moderate (Grade 2), severe (Grade 3), life-threatening (Grade 4) or death (Grade 5).

Tables summarizing the incidence of TEAEs by dose cohort will be generated for each treatment arm with the following:

- TEAEs;
- TEAEs related to CC-122, other combination drug (ibrutinib or obinutuzumab) and CC-122 and/or other combination drug;
- TEAEs of NCI CTCAE grade 3 or 4 by maximum NCI CTCAE grade;
- TEAEs related to CC-122, other combination drug (ibrutinib or obinutuzumab) and CC-122 and/or other combination drug with NCI CTCAE grade 3 or 4 by maximum NCI CTCAE grade;
- TEAEs with death outcome;

- TEAEs with death outcome related to CC-122, other combination drug (ibrutinib and obinutuzumab) and CC-122 and/or other combination drug;
- Serious TEAEs;
- Serious TEAEs related to CC-122, other combination drug (ibrutinib and obinutuzumab) and CC-122 and/or other combination drug;
- TEAEs leading to discontinuation of CC-122, of other combination drug (ibrutinib and obinutuzumab), of CC-122 or other combination drug, of CC-122 and other combination drug;
- TEAEs leading to dose reduction of CC-122, of other combination drug (ibrutinib), of CC-122 or other combination drug, of CC-122 and other combination drug;
- TEAEs leading to dose interruption of CC-122, of other combination drug (ibrutinib and obinutuzumab), of CC-122 or other combination drug, of CC-122 and other combination drug.

As well as

- TEAEs by cycle of onset;
- Febrile Neutropenia, TFR, TLS by cycle of onset and overall;
- TEAEs related to CC-122, other combination drug (ibrutinib or obinutuzumab) and CC-122 and/or other combination drug, by cycle of onset;
- TEAE with onset from second to sixth CC-122 cycle leading to dose reduction/discontinuation of CC-122, of other combination drug (ibrutinib and obinutuzumab), of CC-122 or other combination drug, of CC-122 and/or other combination drug;
- TEAE by CC-122 cycle of onset and leading to dose reduction/discontinuation of CC-122, of other combination drug (ibrutinib and obinutuzumab), of CC-122 and/or other combination drug, of CC-122;
- TEAEs by maximum NCI CTCAE grade;
- TEAEs related to CC-122, other combination drug (ibrutinib or obinutuzumab) and CC-122 and/or other combination drug, by maximum NCI CTCAE grade;
- Common (≥10%) TEAEs;
- Common (≥20%) TEAEs;
- Common (≥10%) TEAEs related to CC-122, other combination drug (ibrutinib and obinutuzumab) and CC-122 and/or other combination drug;
- Common (≥20%) TEAEs related to CC-122, other combination drug (ibrutinib and obinutuzumab) and CC-122 and/or other combination drug;
- Selected TEAE of interest by aggregated terms;
- TEAEs by PT.

Selected TEAEs/ serious AEs (SAEs) of interest as determined by the mechanism of action, known class effects, or TEAEs observed to date will be summarized by treatment arm and dose cohort, and then grade or cycle of onset. Standardized MedDRA queries (SMQs) will be used in the search strategy for some of the selected AEs of special interest, intending to aid in case identification. The groupings of selected AEs,

described by one phrase or topic term will be determined by clinicians based on SMQ or relevant search terms and provided to statistician, prior to database lock.

The selected TEAEs of interest include:

- Cardiac Failure (SMQ)
- Embolic or Thrombotic Events (SMQ) including ATE (Sub-SMQ), VTE (Sub-SMQ), and Mixed Embolic and Thrombotic Events (Sub-SMQ)
- Hemorrhage (SMQ)
- Interstitial Pneumonitis (SMQ)
- Peripheral Neuropathy (SMQ)
- Tumour lysis (SMQ)
- Febrile Neutropenia (PT)
- Tumour Flare (PT)

To facilitate clinical study report writing, a summary table of TEAEs by PTs treatment arm will also be provided.

In addition, the following listings will be provided as well:

- Listing of subjects who had treatment-emergent SAE by treatment arm, dose cohort, subject number, SOC, and PT;
- Listing of subjects who had TEAEs leading to permanent withdrawal of any study drug by treatment arm, dose cohort, subject number, SOC, and PT;
- Listings of subjects who had adverse events leading to study drug reduction or interruption
- Listing of all subjects who died.

Individual subject listing of AEs will be presented as well. In addition, a listing of overdose will be provided.

A summary table for the summary of deaths information will be presented.

11.1.2. Dose-limiting Toxicities (DLTs)

DLT is defined as a treatment-related AE(s) occurring in Cycle 1 (the first 28 days of treatment with CC-122 and combination therapy) that meets one of the criteria defined in the Protocol Section 8.2.7. Subjects will be observed for early DLTs for 28 days following the initiation of CC-122 (for Arm A, Cycle 1 day 1 through Cycle 1 Day 28; for Arm C, Cycle 1 day 9 through Cycle 2 day 8, and for Arm B, Cycle 2 Day 1 through Cycle 2 Day 28) (DLT evaluation period).

A summary table of DLTs during DLT evaluation period will be presented by dose cohort and treatment arm including number and percentage of subjects having a DLT. The percentage of subjects having a DLT is based on the number of subjects who are CC-122 evaluable for DLT Evaluable population. Listing of AEs which meet dose limiting toxicity will be provided.

11.1.3. Adverse Events Subgroup Analysis

As per request of German EC, additional summary tables by SOC and PT will be provided for TEAE and SAE, grouping subjects by gender or age class (≤70 years, >70 years).

11.2. Clinical Laboratory Evaluations

Clinical laboratory tests include:

- Amylase, Lipase, fasting lipid profile, Creatine Kinase, Thyroid-Stimulating Hormone (TSH), Free T4 (fT4), Immunoglobulins (IgG, IgM and IgA only), T-cell subsets.
- Complete Blood Count (CBC): HGB, Hematocrit, Red Blood Cell (RBC) count with indices, WBC 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, ALP, AST/SGOT, ALT/SGPT, and LDH, Uric Acid, Troponin T and B-type Natriuretic Peptide (BNP).
- Beta-2 Microglobulin
- C-Reactive Protein.
- Direct Antiglobulin test (local laboratory only).
- Coagulation tests: Prothrombin Time, INR and, PTT.
- 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 surface Antigen (HBsAg), Hepatitis B core antibody (anti-HBc), and Hepatitis C Virus (HCV) RNA.

Clinical laboratory values will be graded, for applicable tests, according to NCI CTCAE version 4.03 or to IWCLL guidelines for the diagnosis and treatment of CLL (Section 17.8). The value from selected laboratory tests and the change from baseline value will be summarized using descriptive statistics by dose cohort/treatment arm for the timepoints when baseline, maximum or minimum values were observed.

Bidirectional shift tables (low and high) demonstrating the change of NCI CTCAE grades from baseline to worst post-baseline during the treatment period will also be presented by, treatment arm and dose cohort. In addition, frequency count of the worst post-baseline NCI CTCAE grades (low, high) during the treatment period will also be presented by treatment arm and dose cohort.

Summaries of laboratory values by treatment arm, dose cohort, cycle and maximum NCI CTCAE grade will be provided.

Listings of clinical laboratory data, including cardiac laboratory data, with NCI CTCAE grades (if applicable) and abnormal flags (low or high) will be provided.

For some key laboratory tests (HGB, Platelet, ANC,), spaghetti plots for each arm separately will be presented to show the pattern of the laboratory test percent change from baseline over time using the Safety population in dose escalation phase. All non-missing laboratory test values including assessments at scheduled, unscheduled, or EoT visits, will be presented. The X axis will be ticked at the study days, and the Y axis will be the percent change from baseline values. Values for the EoT visit will be included in spaghetti plots but will be displayed for the nominal visit equal to or immediately after the EoT visit.

11.3. Vital Sign Measurements

Vital sign values and change from baseline will be summarized using descriptive statistics by treatment arm, dose cohort, and overall for the timepoints when baseline, maximum or minimum values were observed.

Shift tables demonstrating the changes (low/normal/high) from baseline to worst post-baseline value will be displayed in cross-tabulations by arm and dose cohort for vital sign measurements. Normal ranges given in Table 6 will be used to determine the categories of low, normal, and high.

Data collected for vital sign measurements will be listed.

Table 6: Normal Ranges of Vital Sign Measurements

Test	Normal Range (Unit)
Diastolic Blood Pressure (DBP)	[60, 90] (mmHg)
Systolic Blood Pressure (SBP)	[100, 140] (mmHg)
Pulse	[60, 100] (bpm)
Temperature	[35, 38] (°C)
Respiration	[12, 20] (BPM)

11.4. Electrocardiograms (ECG)

Shift from baseline to worst post-baseline in the overall ECG interpretation ('Normal' 'Abnormal, not clinically significant' and 'Abnormal, clinically significant' will be displayed in cross–tabulations by treatment arm and dose cohort.

A listing of ECG by treatment and dose cohort will be provided.

11.5. Left Ventricular Ejection Fraction (LVEF) Assessment

LVEF assessment values by visit and change from baseline will be summarized using descriptive statistics. Similarly, maximum and minimum post-baseline values and corresponding change from baseline values will be summarized using descriptive statistics.

Shift from baseline to worst post-baseline in the overall LVEF interpretation ('Normal', 'Abnormal, not clinically significant' and 'Abnormal, clinically significant') will be displayed in cross–tabulations by treatment arm and dose cohort.

A summary table of severity grade for LVEF will be provided using levels of "Ejection fraction decreased" from NIC CTCAE (Version 4.03):

- Grade 2 = Resting ejection fraction: 50 - 40%; 10 - 19% drop from baseline.
- Grade 3 = Resting ejection fraction: 39 - 20%; >20% drop from baseline.
- Grade 4 = Resting ejection fraction: <20%.

Moreover, descriptive summary statistics for baseline and worst post baseline LVEF will be provided by dose cohort, overall and treatment arm.

A listing of LVEF by treatment arm and dose cohort will be provided as well.

11.6. Other Safety Assessments

Data collected for other safety assessments including pregnancy status, ophthalmologic examination, tumor lysis and tumor flare will be listed by treatment arm and dose cohort.

Spleen and liver physical examination assessments ('Normal' and 'Abnormal') for Safety population at each visit will be summarized using frequency count by dose cohort, overall and treatment arm. Data collected for physical exam for liver and spleen will be also listed.

[redacted]

12.1. PK and Exposure Response Analyses

During the Dose Escalation phase, intensive PK sampling will be performed in a minimum of 3 subjects in the first cycle in Arm A (Cycle 1, Days 1 and 15). PK parameters will be estimated based on the intensive PK population. Actual sampling times will be used in the calculations of PK parameters by using the non-compartmental analysis (NCA) method. Drug concentrations reported by the bioanalytical laboratory as Below the Quantification Limit (BQL) will be shown as BQL in the data listings. If >50% of results for a given timepoint and dose level, are reported as below the Low Limit of Quantification (LLoQ: 1.0 ng/mL), the mean, median and geometric mean are reported as LLoQ. In these scenarios, the other descriptive statistics are not calculated. Missing concentrations will be treated in PK calculations as if they were never drawn. If a concentration is missing (e.g., because no sample was taken, there was no valid result [including concentrations after dosing which are BQL], there was no detectable peak or the sample was lost), the concentration will not be imputed (i.e., it will remain missing). Every effort will be made to include all concentration data in the analysis. In the event that an actual sample collection time is missing for a certain time point, the planned time may be used for this time point instead.

Pharmacokinetic Plasma Concentrations:

CC-122 plasma concentrations from intensive sampling will be summarized by actual dose level, visit, and nominal time points. In general, geometric mean and the geometric CV (%) will be derived from non-zero concentration values. These results will be tabulated by dose cohort and treatment arms.

CV (%) is calculated as follows: $CV\ (\%) = \frac{StdDev}{mean} \times 100$..

Geometric CV (%) is calculated as follows: $\mathrm{CV}(\%) = 100 \times \sqrt{(\exp(\sigma^2) - 1)}$, where σ^2 denotes the variance of the log-transformed values.

The following figures will be provided by dose cohort using intensive PK population:

- Individual subject's concentration (linear scale and semi-logarithmic scale) over time spaghetti plot;
- Mean and ± Std Dev of concentration (linear scale and semi-logarithmic scale) over time plot;

Note: Mean of 1 ng/mL at timepoint 0 will be imputed when more than 50% of values are below LLOQ.

Summary for Ibrutinib plasma concentration will not be performed due to limit data collected.

Pharmacokinetic Parameters:

For Arm A (CC-122 single agent), intensive PK samples collected are still very limited in time-points and limited in valid concentration values. For Arm B (CC-122 in combination with ibrutinib) and Arm C (CC-122 in combination with obinutuzumab), only sparse PK samples were collected. Therefore, the analyses on the PK parameters stated in protocol (i.e. C_{max}, T_{max}, AUC_t, etc.) will not be performed. Please see the details in Section 15 changes to the statistical analyses section of the protocol.

Following by-subject listings will be provided for all Enrolled population:

- PK blood sampling
- Individual CC-122 plasma concentration for scheduled timepoints
- Individual Ibrutinib plasma concentration for scheduled timepoints

[redacted]

[redacted]

14. INTERIM ANALYSIS

As of Protocol Amendment 7, Phase 2 Expansion Phase will not proceed. The Interim analysis originally planned for the futility analysis of the expansion cohorts will not be conducted.

15. CHANGES TO THE STATISTICAL ANALYSES SECTION OF THE PROTOCOL

- As of Protocol Amendment 7, Phase 2 Expansion Phase will not proceed. Any analysis on the endpoints related to expansion phase, as well as the futility analysis of the expansion cohorts and interim analysis, will not be conducted.
- As intensive PK samples collected are still very limited in timepoints and limited in valid concentration values, analyses on PK (pharmacokinetic) parameter will not be conducted. As a result, the outputs for secondary endpoint "CC-122 pharmacokinetic parameters when administered in combination with Ibrutinib" will not be included in the final CSR package. The analysis on secondary endpoint "Ibrutinib plasma concentrations and/or pharmacokinetic parameters when administered in combination with CC-122" will not be conducted either. However, a by-subject listing for Ibrutinib plasma concentrations for the subjects who received Ibrutinib will be provided.
- In addition, analyses on biomarkers will not be performed and included in the final CSR package. Results might be reported separately. Similarly, the analysis on exploratory endpoint "Response rate, duration of response, and progression free survival in subtypes defined by biomarkers" will not be performed as well.

[redacted]

17. APPENDICES

17.1. Dose Escalation Rules

Table 8: Intrasubject Dose Escalation and Fixed-Doses Cohort Escalation Rules

Arm	No. of subjects recruited	Number of subjects that meet the criteria for DLT	NTD
Arm A[a]	20	> 20 %	
Arm B[b]	3+3	≥2	Yes
Arm C[b]	3+3	≥2	Yes

Notes:
[a] Intrasubject escalation.
[b] Fixed-doses cohort escalation.

17.2. Handling of Dates

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

- **Procedure Dates** are the dates on which given protocol-specified procedure are performed. They include the dates of laboratory testing, physical examinations, tumor scans, etc. They should be present whenever data for a protocol-specified procedure are present and should only be missing when a procedure are marked as NOT DONE in the database. Procedure dates will not be imputed.
- **Log Dates** are dates recorded in CRF data logs. Specifically, they are the start and end dates for AEs and concomitant medications/procedures. They should not be missing unless an event or medication is marked as ongoing in the database. Otherwise, incomplete log dates will be imputed according to the rules in Appendix 17.4. However, in listings, log dates will be shown as recorded without imputation.
- **Milestone Dates** are dates of protocol milestones such as randomization, study drug start date, study drug termination date, study closure date, etc. They should not be missing if the milestone occurs for a subject. They will not be imputed.
- **Outcome Dates** are dates corresponding to study endpoints such as survival, progression, etc. In most cases they are derived either from a milestone (e.g., the survival date is derived from the death date), or a procedure date (e.g., the progression date is derived from the date of the tumor scan that was used to determine progression). They may be subject to endpoint-specific censoring rules if the outcome did not occur but are not otherwise subject to imputation.
- **Special Dates** cannot be classified in any of the above categories and they include the date of birth. They may be subject to variable-specific censoring and imputation rules.

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

17.2.1. Calculation Using Dates

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

Study days after the start day of study drug (referred as DSTART) will be calculated as the difference between the date of interest and the first date of dosing of study drug plus 1 day. The generalized calculation algorithm for relative day is the following:

If TARGET DATE ≥ DSTART then STUDY DAY = (TARGET DATE – DSTART) + 1;

Else use STUDY DAY = TARGET DATE – DSTART.

Note that Study Day 1 is the first day of treatment of study drug (i.e. the earliest date between CC-122, ibrutinib and obinutuzumab). Negative study days are reflective of observations obtained during the baseline/screening period. Note: Partial dates for the first study drug are not imputed in general. All effort should be made to avoid incomplete study drug start dates.

Age (expressed in days) is calculated: AGE = CONSENT – DATE of BIRTH + 1. In practice, age will be transformed into years by dividing the difference by 365.25 days, then truncating. Preference is for using calculated age from clinical database. When not available, calculated age from CRF or Interactive Voice Response System (IVRS) may be used.

Partial birth date: impute missing day as 15th of the month; impute missing month as July; set missing age for missing year.

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

Intervals that are presented in months will be transformed from days to months by using (without truncation) the following conversion formula: MONTHS = DAYS /30.4375

17.2.2. Calculation of Cycles

Study Treatment Cycles

The start date of each cycle is defined as the first day when the subject receives CC-122, ibrutinib or obinutuzumab (non-zero dose) in that cycle. After the start dates are determined, the end date of each cycle is defined as (start date of subsequent cycle-1). The end date of the last cycle will be the last dose date for any study drug, the last dose date of CC-122+2 days or the Day 28 from the start of the last cycle, whichever is later. Any doses of study drug with start/stop dates on or after Day 1 of Cycle 1 but before Day 1 of Cycle 2 will be counted as taken in the Cycle 1. Any doses of study drug taken on or after Day 1 of Cycle 2 but before Day 1 of Cycle 3 will be counted as taken in the Cycle 2, and so forth. Any doses of study drug taken on or after the first day of the last cycle will be counted as taken in the last cycle.

After last cycle in treatment phase, cycles might be defined with 28-days intervals as necessary.

CC-122 Cycles

CC-122 cycle is also defined: CC-122 cycle starts after first CC-122 dose (C1D1 for Arm A, C2D1 for Arm B and C1D9 for Arm C) and each CC-122 cycle lasts 28 days.

17.3. Baseline, Repeated Measurements, and End of Trial

The general conventions for handling baseline, repeated measurements, and End of Trial (EOT) are provided below:

- Baseline for any clinical laboratory test, efficacy endpoints and vital sign is defined as the last value of a specific endpoint measured before the first dose of the IP.

- Baseline values for biomarkers will be the average of non-missing values collected at screening and the last value before first dose of the IP, if both samples are collected. Otherwise, either the values collected at screening or the last value of a specific endpoint measured before the first dose of the IP, whichever is collected, will be used as the baseline. Other pre-dose samples from on-treatment visits after the first dose of the IP will not be used to impute baseline value.
- Central laboratory values will be used; local laboratories will be used only if there is not any central laboratory by first dose date. When there are multiple values for any laboratory test (clinical and biomarker) or vital sign collected at the same visit, the one with last/latest assessment time stamp will be used for data analysis.
- End of trial assessment for a particular endpoint is defined as the last non-missing post-baseline assessment during the study period.
- Adequate efficacy assessment encompasses protocol defined assessments of tumor lesions (lymph nodes, spleen, and liver), peripheral blood test, bone marrow assessment when indicated, and clinical assessment.

17.4. Date Imputation Guideline

This subsection gives guideline on imputation of complete or partial missing AEs, or Concomitant medications start and/or stop dates.

Incomplete Start Date:

Missing day and month

- If the year is the same as the year of the first dosing date, then the day and month of the first dosing date will be assigned to the missing fields.
- If the year is prior to the year of first dosing date, then December 31 will be assigned to the missing fields.
- If the year is after the year of first dosing, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year are the same as the year and month of first dosing date, then the first dosing date will be assigned to the missing day.
- If either the year of the partial date is before the year of the first dosing date or the years of the partial date and the first dosing date are the same but the month of partial date is before the month of the first dosing date, then the last day of the month will be assigned to the missing day.
- If either the year of the partial date is after the year of the first dosing date or the years of the partial date and the first dose date are the same but the month of partial date is after the month of the first dosing date, then the first day of the month will be assigned to the missing day.
- If the stop date is not missing, and the imputed start date is after the stop date, the start date will be imputed by the stop date.

Missing day, month, and year

- No imputation is needed, the corresponding AE will be included as TEAE.

Incomplete Stop Date: If the imputed stop date is before the start date, then the imputed stop date will be equal to the start date.

Missing day and month

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

Missing day only

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

[redacted]

[redacted]

[redacted]

[redacted]

17.6. Laboratory Data Handling

For absolute and percent values of basophils, eosinophils, lymphocytes, monocytes, and neutrophils, the missing absolute values will be imputed by (corresponding non-missing percent values × WBC counts), while the missing percent values will be imputed by (corresponding non-missing absolute values ÷ WBC counts) ×100. If both absolute and percent values are missing, no imputation will be performed.

The following data handling rules for laboratory parameters are for data analysis purpose (Tables and Figures). All original data will be presented as is in the data listings.

Table 11: Data Handling Conventions for Laboratory Parameters

Case	Convention	Example Data
values recorded as "<xx"	Set the numerical value to one tenth less in the next digit/decimal point	Immunoglobulin M (Serum) recorded as "<0.20" (g/l), set the numerical value to 0.199
values recorded as ">xx"	Set the numerical value to one tenth more in the next digit/decimal point	Creatinine clearance recorded as "> 60" (ml/min), set the numerical value to 60.1

17.7. Study Procedures

Please refer to Protocol Section 5 – Table of Events

17.8. Laboratory Abnormalities Toxicity Grading as Recommended by IWCLL Guidelines

Subjects will be evaluated for laboratory abnormalities as recommended by the IWCLL guidelines for the diagnosis and treatment of chronic lymphocytic leukemia [redacted] as listed below:

Table 13: Grading Scale for Hematologic Toxicity in Chronic Lymphocytic Leukemia Studies

Grade[a]	Decrease in Platelets[b] or HGB[c] (nadir) From Pre-treatment Value (%)	Absolute Neutrophil Count[d] (mm^3) (nadir)
0	No change to 10%	≥ 2,000
1	11% - 24%	≥ 1,500 and < 2,000
2	25% - 49%	≥ 1,000 and < 1,500
3	50% - 74%	≥ 500 and < 1,000
4	≥ 75%	< 500

Notes:

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

[b] Platelet counts must be below normal levels for Grades 1-4. If, at any level of decrease the platelet count is < 20,000/mm3, this will be considered Grade 4 toxicity, unless a severe or life-threatening decrease in the initial platelet count (e.g., 20,000/ mm3) was present pre-treatment, in which case the subject is not evaluable for toxicity referable to platelet counts.

[c] Hemoglobin (HGB) levels must be below normal levels for Grades 1-4. Baseline and subsequent HGB determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity but should be documented.

[d] If the absolute neutrophil count (ANC) reaches less than 1,000/ mm3, it should be judged to be Grade 3 toxicity. Other decreases in white blood cell count, or in circulating granulocytes, are not to be considered, since a decrease in white blood cell count is a desired therapeutic end point. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. The use of granulocyte colony-stimulating factor (G-CSF) is irrelevant for the grading toxicity but should be documented.

[redacted]

17.9. Cumulative Illness Rating Scale (CIRS)

The CIRS used in this protocol is designed to provide an assessment of recurrent or ongoing chronic comorbid conditions, classified by 14 organ systems. Please specify the name of the conditions within an organ system. If there are two or more illnesses/impairments in one organ system, the illness/impairment with the highest severity will be evaluated. Please take into account that CLL-induced discomfort, symptoms, or disability should not be considered. If additional explanation would be helpful, text comments may be inserted. The sum of all individual organ scores should be calculated.

Table 14: Cumulative Illness Rating Scale

Please insert the appropriate grade of illness/impairment (0-4):		
Organ System	**If illness/Impairment Present, please specify:**	**Score (0-4)**
Cardiac		
Vascular		
Hematological/Immunological		
Respiratory		
Ophthalmological/Otolaryngological		
Upper Gastrointestinal		
Lower Gastrointestinal		
Hepatic/Pancreatic		
Renal		
Gynecological/Urological		
Dermatological/Musculoskeletal		
Neurological		
Endocrine/Metabolic		
Psychiatric		
Total Score:		

For the severity rating, please use the scoring guidelines shown in the table below, considering the magnitude of symptoms, how manageable the condition is, and the extent of intervention required. A score of 0 is given if organ system is not compromised (i.e. no problem).

Table 15: CIRS Rating Scale

Score	Severity	Findings
1	Mild	• Mild discomfort, symptoms or disability • Easy to control • Requiring either no therapy/medication or only as needed
2	Moderate	• Moderate discomfort, symptoms or disability • Manageable • Requiring daily treatment or first-line therapy
3	Severe	• Severe discomfort, symptoms or disability • Hard to control • Requiring second-line therapy or multiple medications
4	Extremely severe	• Life threatening, permanently disabling disability, causing organ failure • Poorly manageable • Requiring urgent intervention or resistant to therapy

Abbreviation: CIRS=Cumulative Illness Rating Scale