Statistical Analysis Plan

Protocol Title: A Phase 1/2, Multicenter, Open-label, and Dose-escalation Study of ACP-196 in Subjects with Chronic Lymphocytic Leukemia, Richter's Syndrome or Prolymphocytic Leukemia

Protocol Number: ACE-CL-001

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Version / Date: Final / February 24, 2017
Amendment 1 / August 25th, 2021

DocuSign Envelope ID: DACE0574-8EA2-416A-A157-F03B0A6F2A90

A Phase 1/2, Multicenter, Open-label, and Dose-escalation Study of ACP-196 in Subjects with Chronic Lymphocytic Leukemia, Richter's Syndrome or Prolymphocytic Leukemia

Approval Page

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Final Version: PPD

Amendment 1:

Approval:

PPD

25 August 2021 | 11:20 PDT
Date

26 August 2021 | 13:49 ADT
Date

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1.0 INTRODUCTION

This statistical analysis plan (SAP) provides details of the statistical analyses that have been outlined within the protocol for study ACE-CL-001 Protocol Amendment 13 (dated August 25th, 2021), which is entitled "A Phase 1/2, Multicenter, Open-label, and Dose-escalation Study of ACP-196 in Subjects with Chronic Lymphocytic Leukemia, Richter's Syndrome or Prolymphocytic Leukemia". From here on, acalabrutinib will be used in place of ACP-196 in this document.

The scope of the SAP will cover safety and efficacy analyses. Pharmacokinetic (PK) and pharmacodynamic (PD) analyses will be provided in the respective reports. Analysis of electrocardiogram (ECG) data will be performed by an Acerta designated vendor and a separate detailed report will be included to the interim Clinical Study Report (CSR).

If there are differences between protocol specified analyses and the SAP, the SAP will supersede protocol. Major differences will be noted and rationale will be provided in Section 13.0 of this document and the interim CSR.

To support the acalabrutinib New Drug Application (NDA) for relapsed or refractory Mantle Cell Lymphoma (MCL) in 2017, an interim CSR of study ACE-CL-001 was provided consisting of safety analyses for all disease subgroups and efficacy analyses for the relapsed or refractory (RR) disease subgroup as assessed by the investigator. Independent Review Committee (IRC) assessment was not available at this time and was not included in the interim CSR per Protocol Amendment 8 (dated 08 January 2016).

To support the acalabrutinib supplemental New Drug Application (sNDA) for previously untreated and relapsed or refractory chronic lymphocytic leukemia (CLL) in 2019, an interim CSR of study ACE-CL-001 with updated datasets was provided consisting of safety analyses and efficacy analyses for the treatment naïve (previously untreated) and relapsed or refractory (RR) disease subgroup as assessed by the investigator. The requirement of IRC assessment of response was removed in Protocol Amendment 10 (dated 22 February 2018).

2.0 STUDY OBJECTIVES

The primary objectives of this study are to:

- Establish the safety and the maximum tolerated dose (MTD) of orally administered acalabrutinib in subjects with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).
- Determine pharmacokinetics (PK) of orally administered acalabrutinib and identification of its major metabolite
- The secondary objective is to evaluate tumor response by overall response rate (ORR), duration of response (DOR), and progression-free survival (PFS).

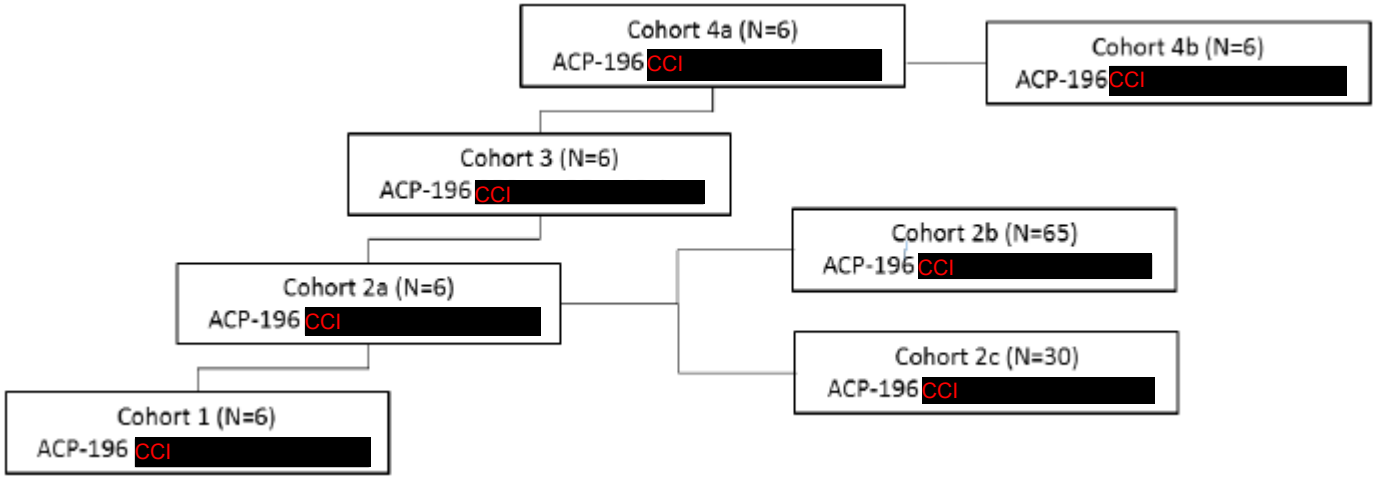
- CCI [redacted]

3.0 OVERALL STUDY DESIGN

This study is a Phase 1/2, multicenter (approximately 15 global centers), open-label, nonrandomized, sequential group, dose-escalation study. The phase 1 portion is a dose escalation to establish the maximum tolerated dose (MTD) and the phase 2 expansion portion is to expand sample size on selected dose levels/regimens and additional indications. Table 2 summarizes the revision history of dose regimen and revision history of sample size from protocol original version to amendment 8. For more details on study design, please refer to protocol. Protocol amendments and revision dates are as follows:

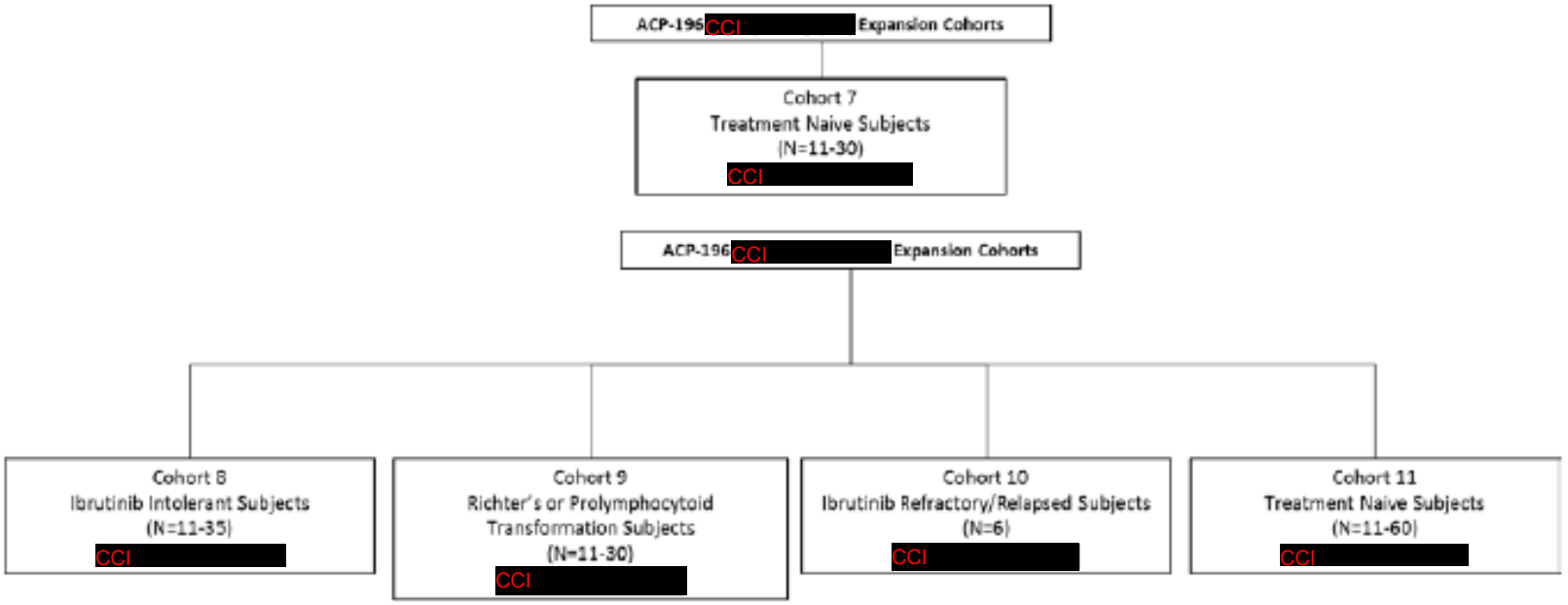
- Original – 01 October 2013
- Amendment 1 – 18 December 2013
- Amendment 2 – 06 May 2014
- Amendment 3 – 03 July 2014
- Amendment 4 – 22 September 2014
- Amendment 5 – 14 February 2015
- Amendment 6 – 01 May 2015
- Amendment 7 – 14 December 2015
- Amendment 8 – 08 January 2016
- Amendment 9 – 30 March 2017
- Amendment 10 – 22 February 2018
- Amendment 11 – 17 January 2020
- Amendment 12 – 18 January 2021
- Amendment 13 – 25 August 2021

STUDY SCHEMA FOR DOSE-ESCALATION COHORTS



Note: No DLTs occurred during dose escalation and the MTD was not reached. Under Amendment 4, subjects in Cohort 3 were switched to CCI Under Amendment 5, subjects in Cohort 1, Cohort 2a, and Cohort 4a were switched to CCI Under Amendment 6, subjects in Cohort 2c and in Cohort 4b CCI were switched to CCI.
Abbreviations: bid = twice daily; DLT = dose-limiting toxicity; MTD = maximum tolerated dose; qd = once daily

STUDY SCHEMA FOR TREATMENT SUBGROUPS (DISEASE SUBGROUP)



Note: Under Amendment 6, subjects in Cohort 7 were switched to CCI
Abbreviations: bid = twice daily; qd = once daily

4.0 SAMPLE SIZE CONSIDERATION

Phase 1 Dose Escalation

The design of the Phase 1 (ie, dose-escalation portion) of the study was not determined based on power considerations. The MTD was defined as the largest daily dose for which < 33% of the subjects experienced a DLT during Cycle 1. No DLT was observed during the dose escalation phase of the study and the MTD was not reached. DLT was reviewed at the time all subjects within each escalation cohort completing one cycle of treatment. The summary of review and findings are filed at Acerta's Trial Master File.

Phase 2 Expansion

Protocol Original version to Amendment 2: There was no expansion cohort in these protocol versions. Original version included dose escalation cohorts 1, 2a, 2b escalation, and 3. Amendment 2 added dose escalation cohorts 4a and 4b. All cohorts were relapse or refractory (RR) subjects.

Protocol amendment 3: Expansion cohort 7: treatment naive (TN), 8a: ibrutinib intolerant (II), 9 Richter's Syndrome or Prolymphocytic Leukemia (RS/PLL) with 8 to 12 subjects each, and cohort 10 (ibrutinib RR) with 12 to 16 subjects were added.

Protocol amendment 4: Existing subjects in cohort 8a (II) were switched from dose level CCI and new subjects enrolled to this cohort received CCI (cohort 8b) starting from Cycle 1 Day1. Expansion cohorts 2b expansion, 2c (RR), 8b (II), and 11 (TN) were added. The sample size for all expansion cohorts were changed to 30 subjects each based on Simon's 2-stage design.

Each cohort of the Phase 2 expansion portion will test the null hypothesis that the ORR is ≤ 10% against the alternative hypothesis that it is ≥ 35%. Using Simon's optimal 2-stage design (Simon 1989), a total sample size of 30 subjects per cohort has power = 0.90 to achieve a 1-sided significance level of ≤ 0.025. In Stage 1, 11 subjects will be enrolled per cohort; if ≥ 2 subjects (18%) achieves an objective response of a partial remission (PR)/PR with lymphocytosis (PRL) or better within the first 4 cycles of treatment, then that cohort will continue to full enrollment. Under the Simon 2-stage design, an ORR of ≥ 23% (ie, ≥ 7 subjects responding of 30 subjects evaluated) will achieve a significance level of ≤ 0.025. Using an exact binomial confidence interval (CI), an ORR of 23% (ie, 7 subjects responding of 30 subjects evaluated) will achieve a 2-sided 90% lower bound of 11.5%. Considering the planned expansion cohort size of 30 subjects, Table 1 shows the 2-sided exact 90% binomial CIs on the true response rate for the range of possible values for the observed response rate.

Table 1. Two-Sided Exact 90% CIs for ORR in Expansion Cohorts (N=30)

		90%CI	
Responses, n	**Response Rate, %**	**Lower Bound**	**Upper Bound**
0	0%	0.0%	9.5%
1	3.3%	0.2%	14.8%
2	6.7%	1.2%	19.6%
3	10.0%	2.8%	23.9%
4	13.3%	4.7%	27.9%
5	16.7%	6.8%	31.9%
6	20.0%	9.1%	35.7%
7	23.3%	11.5%	39.4%
8	26.7%	14.0%	43.0%

Abbreviation: CI = confidence interval, ORR = overall response rate

Protocol amendment 5: The sample size was increased from 30 subjects to 200 subjects for cohort 2b (RR) and to 60 subjects for cohort 11 (TN) to provide safety and efficacy data in support of the Phase 3 program of acalabrutinib in CLL.

Protocol amendment 6: No change on sample size.

Protocol amendment 7: The sample size was decreased from 200 subjects to 65 subjects for cohort 2b (RR) which is considered sufficient to meet the primary objective of this study. The sample size for cohort 8b (II) was increased from 30 subjects to 35 subjects to obtain additional safety and efficacy data in ibrutinib intolerant population.

Protocol amendment 8-13: No change on sample size.

A total of approximately 286 eligible subjects were planned to be enrolled in this study.

Table 2. Summary of Dose Regimen and Sample Size

Cohort	Dose Regimen	Treatment Phase	Disease Subgroup	Planned Sample Size*	Protocol Version the Cohort First Added	Revision History of Dose Regimen	Revision History of Sample Size
1	CCI [redacted]	Escalation	RR	6	Original	CCI [redacted]	
2a		Escalation	RR	6	Original		
3		Escalation	RR	6	Original		
4a		Escalation	RR	6	A2		
2b		Escalation / Expansion	RR	65	A2/A4		A2 (N=6) dose escalation → A4 (N=30) expansion → A5 (N=200) → A7 (N=65)
4b		Escalation	RR	6	A2		
2c		Expansion	RR	30	A4		
7		Expansion	TN	30	A3		A3 (N=8-12) → A4 (N=30)
11		Expansion	TN	60	A4		A4 (N=30) → A5 (N=60)
8a		Expansion	Ibr. Intol.	8-12	A3		A3 (N=8-12) → A4 subjects switched to100 mg bid
8b		Expansion	Ibr. Intol.	35	A4		A 4 (N=30) → A7 (N=35)
9		Expansion	RS/PLL	30	A3		A3 (N=12) → A4 (N=30)
10		Expansion	Ibr. RR	6	A3		A3 (N=16) → A4 (N=30) → A7 (N=6)

* Planned sample size was based on the sample size in Amendment 8 except Cohort 8a, which was lumped with Cohort 8b into one cohort and subsequently renamed "Cohort 8 Ibrutinib Intolerant CCI [redacted]" in Amendment 4.
RR = relapse or refractory, TN = treatment naïve, Ibr. Intol. = ibrutinib intolerant, RS = Richter's syndrome, PLL= prolymphocytic leukemia, Ibr. = ibrutinib
bid = twice daily, qd = once daily

5.0 ANALYSIS POPULATIONS

Analysis populations will be defined in the following sections. In each analysis population, subjects will be analyzed at the dose level they were assigned to at the time of enrollment. The safety analyses will be performed on the All Treated Population. Primary efficacy analyses for ORR and DOR will be based on the Efficacy Evaluable Population. PFS and time to initial response analysis will be based on the All Treated Population. Response will be assessed by investigators. Response assessed by IRC is not available for the interim CSR but will be analyzed and included in the final CSR.

5.1 Enrolled Population

The Enrolled Population will include all subjects who completed the enrollment procedures as specified in the Enrollment Procedures section (Section 3.4.5) of the protocol.

5.2 All Treated Population

The All Treated Population will include all enrolled subjects who received ≥1 dose of study drug.

5.3 Efficacy Evaluable Population

The Efficacy Evaluable Population will include all subjects in the All Treated Population who had ≥1 response assessment after the first dose of study drug.

6.0 STATISTICAL METHODS

6.1 Data Presentation

Tables and figures will be summarized by disease subgroup and cohort unless otherwise specified.

No formal tests of hypotheses will be performed. P-values, if presented, will be provided for descriptive purpose. Descriptive statistics (number of subjects, mean, and standard deviation, median, minimum, and maximum) will be presented for continuous variables including baseline demographic, disease characteristics, study drug administration, efficacy and safety outcomes. Categorical variables will be summarized as the number and percentage of subjects per category. Confidence intervals [CIs] may be included as appropriate.

6.2 General Conventions

Baseline is defined as the last measurement taken prior to the first dose of study drug administration. *Post baseline* is defined as a measurement taken after the first dose of study drug administration.

Study Day 1 is defined as the date of first dose. For visits (or events) that occur on or after first dose date, study day is calculated as (date of visit [event] – date of first dose + 1). For visits (or events) that occur prior to first dose date, study day is calculated as (date of visit [event] – date of first dose). There is no Study Day 0.

Lab data summary will be based on central labs. Local labs will be used if central labs are not available. Central labs will use reference ranges provided by the central lab and local labs will use the reference ranges provided by local labs.

6.3 Analysis Windows

For parameters summarized by visit, an analysis window will be assigned to each nominal visit. Each assessment will be assigned to an analysis visit based on the analysis window the assessment date will fall in. Details are defined in Appendix A.

6.4 Missing Data Handling

No imputation for missing values of efficacy endpoints. Imputation for missing dates such as AE start or end dates, prior and concomitant medication start or end dates will be documented in the programming specifications.

7.0 SUBJECT DISPOSITION

The number and percentage of subjects in Enrolled Population, All Treated Population, Efficacy Evaluable Population, discontinuing treatment and reasons, and not completing the Safety follow up and reasons, and time on study will be presented.

8.0 IMPORTANT PROTOCOL DEVIATIONS

Important Protocol Deviations (IPDs) categories are defined and managed by the study team during the IPD reviews throughout the study before database lock. These definitions of IPD categories, sub-category codes and descriptions will be used during the course of the study. The final IPD list is used to produce the summary table and by-subject listing for IPDs.

9.0 DEMOGRAPHICS AND BASELINE DISEASE CHARACTERISTICS

The following variables collected at baseline will be presented:

- Demographics
  - Age (years)
    - Descriptive statistics
    - <65 vs. ≥65 years

- <70 vs. ≥70 years
- Sex (male, female)
- Race
  - American Indian/Alaskan Native, African American/Black, Asian, Caucasian/White, Native Hawaiian/Other Pacific Islander or Other
  - White vs. Non-white
- Ethnicity (Hispanic or Latino, Non-Hispanic or Latino)
- Enrollment by region (United States, Ex-United States)

➢ Baseline disease characteristics

- Height
- Weight
- Histology
  - For RR, TN, ibrutinib intolerant, and ibrutinib relapse/refractory
    - CLL
    - SLL
  - For RS/PLL
    - CLL transformed to DLBLC
    - CLL transformed to PLL
    - FL transformed to DLBCL
- Time since initial CLL diagnosis to first dose (years) (not applicable to RS/PLL)
- Time since initial CLL diagnosis to transformation (years) (RS/PLL only)
- Time since transformation to first dose (years) (RS/PLL only)
- ECOG performance status
- Chromosomal abnormalities
  - Deletion 17p: 17p13 (TP53)
  - Deletion 11q: 11q22.3 (ATM)
  - Unmutated IGHV
- β2-microglobulin
  - >3 vs. ≤3 mg/L
  - >3.5 vs. ≤3.5 mg/L

- Bulky disease (not applicable for RS/PLL) – defined as if at least one dimension of the lymph node measurement is
  - ≥5 cm
  - ≥10 cm
- Rai stage – derived based on variables collected at screening visit using the criteria described in Appendix B. Additionally, Rai stage collected on the eCRF will be summarized. Rai stage is not applicable to RS/PLL cohort.
- B symptom – weight loss, fever, night sweats
- Number of prior systemic therapy
  - Descriptive statistics
  - <3 vs. ≥3
- Type of prior systemic therapy
- Time since most recent systemic therapy (months)
- Cytopenia
  - Absolute neutrophil count (ANC) ≤1.5x10^9/L
  - Hemoglobin ≤11g/dL
  - Platelet ≤100x10^9/L
  - Hemoglobin ≤11g/dL or platelet ≤100x10^9/L
  - Any of the above
- ANC (10^9/L)
  - Descriptive statistics
  - ANC >1.5 to <2 x10^9/L
- Absolute lymphocyte count (ALC) (10^9/L)
- Hemoglobin (g/dL)
- Platelets (10^9/L)
- Sum of product diameter (SPD) (cm^2)
- Baseline hepatomegaly per PE
- Baseline splenomegaly per PE

10.0 MEDICAL HISTORY

Medical history will be summarized by system organ class (SOC) and preferred term (PT). Recurrence of ibrutinib related adverse events prior to first dose of study drug will be summarized by preferred term in a shift table for ibrutinib intolerant cohort (8a and 8b) only.

11.0 EFFICACY ANALYSIS

Response will be assessed by investigators based on Hallek 2008 with incorporation of the clarification for treatment-related lymphocytosis per Cheson 2012 for CLL/SLL and Cheson 2014 for Richter's Syndrome.

11.1 Overall Response Rate (ORR)

ORR is the proportion of subjects who achieve complete remission (CR), CR with incomplete marrow recovery (CRi), or partial remission (PR) while on treatment before the initiation of new anti-cancer therapy or stem cell transplant. The corresponding 95% CIs using exact binomial distribution will be provided.

ORR will be summarized using Efficacy Evaluable Population and All Treated Population. Efficacy Evaluable Population is the primary analysis population.

For CLL disease subgroups (ie, except RS/PLL disease subgroup), ORR including PRL as a response will also be summarized in the same fashion.

11.2 Progression-free Survival (PFS)

PFS is defined as the time from the date of first dose to the date of first disease progression or death due to any cause. If a subject does not experience any disease progression or death, the subject will be censored at the date of last adequate assessment (censoring date). If a subject receives an autologous or allogeneic stem cell transplant, the subject will be censored at the date of transplant. If a subject starts new anticancer therapy before disease progression or death, the subject will be censored at the date of last adequate assessment prior to receiving the new anticancer therapy. Adequate assessment is defined as physical examination (PE) and complete blood count (CBC) or computed tomography (CT) for CLL disease subgroups (or PET-CT for RS/PLL disease subgroup) and CBC. If a subject does not have any adequate assessment after first dose, the subject will be censored at Day 1.

PFS is calculated as date of disease progression or death (censoring date for censored subjects) - first dose date + 1.

Events and censoring rules for PFS are summarized as follows:

Situation	Outcome	Date	Event Description/ Censoring Reason
Documented PD	Event	Earliest date of disease	PD

		assessment documenting PD	
Death	Event	Date of death	Death
Start of new anticancer therapy before documented PD or death	Censored	Date of last adequate assessment prior to receiving the new anticancer therapy	New anticancer therapy
Start of transplant	Censored	Date of transplant	Transplant
Withdrawal of consent before documented PD or death	Censored	Date of last adequate disease assessment	Withdrawal of consent
Loss to follow-up before documented PD or death	Censored	Date of last adequate disease assessment	Loss to follow-up
No documented PD or death and the reason for not completing Safety Follow-up visit is "Other"	Censored	Date of last adequate disease assessment	Other: *specify*
No documented PD or death at the time of data cutoff	Censored	Date of last adequate disease assessment	Data cutoff
No post-baseline adequate disease assessments	Censored	Date of first dose	No post-baseline adequate disease assessments

Kaplan-Meier (KM) curve will be used to estimate the distribution of PFS. Median PFS and the 95% confidence limits and PFS rates for selected landmarks with 95% confidence intervals will be reported. Number of progressions, deaths, and censored events by reason will be summarized.

11.3 Duration of Response (DOR)

DOR is defined as the time from the date of achieving the first CR, CRi, or PR to the date of disease progression or death due to any cause, whichever comes first. Subjects who do not have a disease progression or death will be censored using the same rule for PFS as described in Section 11.2.

DOR is calculated as date of disease progression or death (censoring date for censored subjects) – date of achieving the first CR, CRi, or PR + 1.

Kaplan-Meier (KM) curve will be used to estimate the distribution of DOR. The same summary statistics for PFS will be presented for DOR.

For CLL disease subgroups (ie, except RS/PLL disease subgroup), DOR including PRL as one of the responses will also be summarized in the same fashion.

11.4 Time to Initial Response

Time to initial response of PR or better will be calculated as (date of first PR or better – date of first dose + 1) / 30.4376 and summarized using descriptive statistics. Time to initial response of PRL or better for CLL disease subgroups (ie, except RS/PLL disease subgroup) will also be summarized in the same fashion.

11.5 Subgroup Analysis

CCI

[redacted]

12.0 SAFETY ENDPOINTS

Safety will be assessed by evaluation of treatment-emergent adverse events, laboratory values, vital signs measurements, ECG results and physical exams.

12.1 Adverse Events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA v 24.0) reporting system. Treatment-emergent AEs are defined as those events that occur on or after the first dose of study drug, through the treatment phase, and within 30 days following the last dose of study drug.
The occurrence of treatment-emergent adverse events (TEAEs) and serious TEAEs will be presented respectively by SOC and PT. If a subject experiences the same event more than once, the event will be counted only once with the greatest severity. Additionally, TEAEs and serious TEAEs will be presented by relationship and by worst severity.

Fatal (Grade 5) AEs, AEs leading to study drug discontinuation, AEs leading to study drug interruption, and AEs leading to study drug modification will be summarized.

Events of clinical interest (ECI) will be summarized. Definition of each ECI is listed in Integrated Summary of Safety (ISS), Appendix B.

For ibrutinib intolerant cohorts (8a and 8b), ibrutinib related AE will be tabulated.

12.2 Hematology, Chemistry, and Immunology Parameters

Selected laboratory parameters such as AST, ALT, bilirubin, amylase, and lipase will be graded based on CTCAE 4.03. Hematologic toxicities in CLL patients will be graded by Hallek (2008) as specified in Appendix C and CTCAE 4.03. Shift tables will be presented to summarize grade shift from baseline to maximum post baseline grade. Graphs will be presented for mean or median of selected lab parameters over time as appropriate.

T/B/NK/Monocytes Cell Counts
Plot for mean change over time and standard error of mean (SEM) at each time point will be presented for selected flow cytometry testing parameters, $CD4^+$, $CD8^+$, NK cells, and Monocytes.

Serum Immunoglobulin
For IgG, IgM, and IgA levels, descriptive statistics will be presented at baseline, last post baseline, minimum post baseline, and maximum post baseline. Changes from baseline at each of the last, minimum, and maximum post baseline time points will be summarized.

Molecular Markers

Molecular markers are collected at screening visit. Parameters to be summarized include 11q13 (CCND1), 13q14(D13S319), 13q34, 6q23 (MYB), ZAP70 (CLL), BCL6, Blasts Gate, CEP 12, CEP6(D6Z1), Granulocyte Gate, Immunoglobulin Heavy locus (IGH), Lymph Gate, MYC, MYD88, Monocyte Gate, Notch 1, Plasma Gate, SF3B1, Viability.

12.3 B Symptoms

Descriptive statistics will be presented for B-symptoms. For subjects who were symptomatic at baseline, sample size and percent of subjects with resolution at post baseline will be summarized by visit. For those who were as asymptomatic at baseline, sample size and percent of subjects with onset of symptoms at post baseline will also be summarized by visit.

12.4 Vital Signs and Physical Examinations

For each vital sign measurement, descriptive statistics will be presented at baseline, last post baseline, minimum post baseline, and maximum post baseline. Change from baseline at each of the last, minimum, and maximum post baseline time points will be summarized.

Findings of abnormal physical examinations will be tabulated by body system at each visit.

12.5 Prior and Concomitant Medications

Prior and concomitant medications will be coded according to the World Health Organization (WHO) drug dictionary. Medications started or ended prior to first dose will be considered as prior medications. Concomitant medication is defined as all medications used on or after the first dose, through the treatment phase, and for 30 days following the last dose of study drug. Using this definition, a medication can be classified as both prior and concomitant. Medications with completely missing start and stop dates will be considered as both prior and concomitant medications.

Appendix D shows the prior and concomitant medication flags for various scenarios. The number and percentage of subjects will be presented by anatomical therapeutic chemical (ATC) classification system Level 2 and preferred term.

12.6 Study Drug Exposure

- Duration of exposure (months) is defined as (last dose date – first dose date + 1) / 30.4375
- Total cumulative dose (g) is defined as total amount of dose received during the study period
- Average daily dose (mg/day) is defined as (actual cumulative dose (mg) / duration of exposures)
- Relative dose intensity is defined as (total cumulative dose (mg) / (duration of exposure (days) * 1 (g) * 2) *100) Descriptive statistics will be presented for these values. Relative dose intensity will be calculated for Cohort 2b, 2c, 9, and 10 in which the intended dose regimen/level were never changed per protocol throughout the study.

12.7 Eastern Cooperative Oncology Group (ECOG) Performance Status

Shift of ECOG from baseline to the worst score during the treatment will be summarized in a shift table.

12.8 Electrocardiogram (ECG)

ECG will be done in triplicate (≥ 1 minute apart) at screening for all subjects. The intensive ECG schedule as specified in the Schedule of Assessments of the protocol is only for the subjects in the dose escalation portion of the study. The intensive ECG data analysis will be performed by an Acerta designated vendor and a separate detailed report will be included as part of the CSR. .

13.0 DEVIATIONS FROM PROTOCOL AND OTHER ISSUES

Time to initial response is not specified as an efficacy endpoint in the protocol. Since it provides information about the onset of response, it is added to the SAP as an efficacy endpoint.

If there are changes to the planned analyses described in the SAP, they will be described in the clinical study report.

14.0 REFERENCES

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Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials 1989; 10:1-10.

15.0 APPENDICES

Appendix A: Analysis Windows

Tumor assessment/CT/SPD				
			Analysis Window (Study Day)	
Nominal Visit	Study Day	Nominal Month	Lower (inclusive)	Upper (inclusive)
C2D28	56	2	2	84
C4D28	112	4	85	140
C6D28	168	6	141	210
C9D28	252	8	211	294
C12D28	336	11	295	378
C15D28	420	14	379	462
C18D28	504	17	463	546
C21D28	588	19	547	630
C24D28	672	22	631	756
C30D28	840	28	757	924
C36D28	1008	33	925	1092
C42D28	1176	39	1093	1260
C48D28	1344	44	1261	1428
C54D28	1512	50	1429	1596
C60D28	1680	55	1597	

Hematology / Chemistry				
			Analysis Window (Study Day)	
Nominal Visit	Study Day	Nominal Month	Lower (inclusive)	Upper (inclusive)
C1D1	1	0		1
C1D28	28	1	2	42
C2D28	56	2	43	70
C3D28	84	3	71	98
C4D28	112	4	99	126
C5D28	140	5	127	154
C6D28	168	6	155	210

C9D28	252	8	211	294
C12D28	336	11	295	378
C15D28	420	14	379	462
C18D28	504	17	463	546
C21D28	588	19	547	630
C24D28	672	22	631	714
C27D28	756	25	715	798
C30D28	840	28	799	882
C33D28	924	30	883	966
C36D28	1008	33	967	1050
C39D28	1092	36	1051	1134
C42D28	1176	39	1135	1218
C45D28	1260	41	1219	1302
C48D28	1344	44	1303	1386
C51D28	1428	47	1387	1470
C54D28	1512	50	1471	1554
C57D28	1596	52	1555	

Amylase / Lipase				
			Analysis Window (Study Day)	
Nominal Visit	**Study Day**	**Nominal Month**	**Lower** (inclusive)	**Upper** (inclusive)
C1D1	1	0		1
C1D28	28	1	2	42
C2D28	56	2	43	70
C3D28	84	3	71	98
C4D28	112	4	99	126
C5D28	140	5	127	154
C6D28	168	6	155	210
SFU			Last dose date +15	Last dose date +45

Serum Ig, T cell (CD4, CD8), NK and monocyte counts				
			Analysis Window (Study Day)	
Nominal Visit	**Study Day**	**Nominal Month**	**Lower** (inclusive)	**Upper** (inclusive)
C1D1	1	0		1
C2D28	56	2	2	154
C9D28	252	8	155	336
C15D28	420	14	337	504
C21D28	588	19	505	672
C27D28	756	25	673	840
C33D28	924	30	841	1008
C39D28	1092	36	1009	1176
C45D28	1260	41	1177	1344
C51D28	1428	47	1345	1512
C57D28	1596	52	1513	

B Symptoms				
			Analysis Window (Study Day)	
Nominal Visit	**Study Day**	**Nominal Month**	**Lower** (inclusive)	**Upper** (inclusive)
C1D1	1	0		1
C2D15	43	1	2	64
C3D28	84	3	65	98
C4D28	112	4	99	126
C5D28	140	5	127	154
C6D28	168	6	155	210
C9D28	252	8	211	294
C12D28	336	11	295	378
C15D28	420	14	379	462
C18D28	504	17	463	546
C21D28	588	19	547	630
C24D28	672	22	631	714
C27D28	756	25	715	798
C30D28	840	28	799	882
C33D28	924	30	883	966

C36D28	1008	33	967	1050
C39D28	1092	36	1051	1134
C42D28	1176	39	1135	1218
C45D28	1260	41	1219	1302
C48D28	1344	44	1303	1386
C51D28	1428	47	1387	1470
C54D28	1512	50	1471	1554
C57D28	1596	52	1555	

Appendix B: Rai Stage Derivation Criteria

Stage	Lymphocytosis	Lymphadenopathy	Hepatomegaly or splenomegaly	Anemia	Thrombocytopenia
0	1	0	0	0	0
I	1	1	0	0	0
II	1	any	1	0	0
III	1	any	any	1	0
IV	1	any	any	any	1

1 = yes, 0 = no, any = yes or no

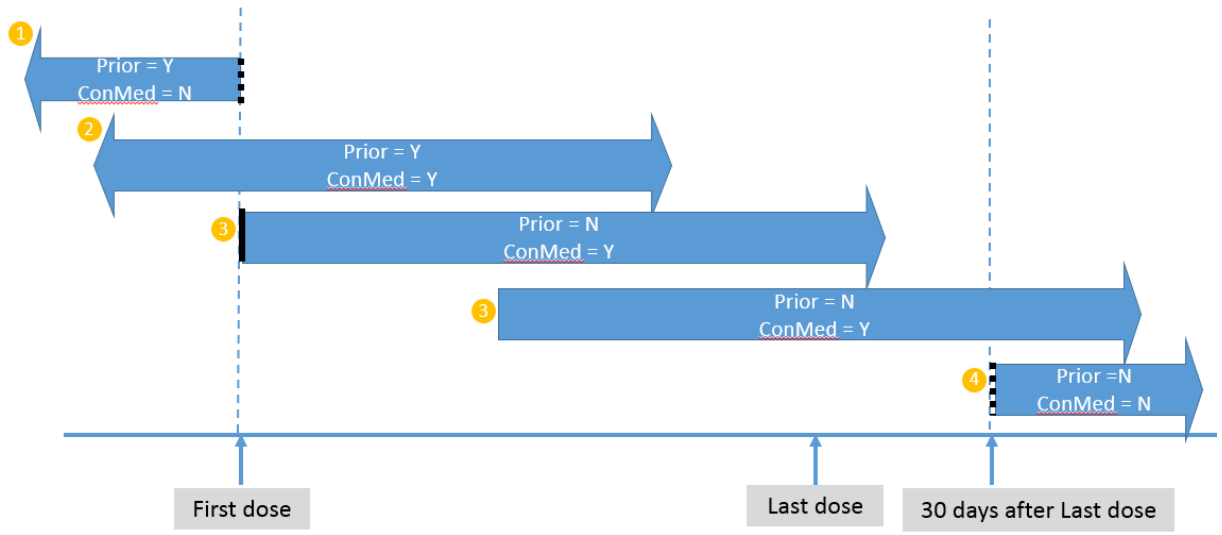
Appendix C: Grading Scale for Hematologic Toxicity in CLL (Hallek 2008)

Grade[1]	Decrease in platelets[2] or Hb[3] (nadir) from pretreatment value	Absolute neutrophil count/μL[4] (nadir)
0	No change to 10%	≥2000
1	11%-24%	≥1500 and <2000
2	25%-49%	≥1000 and <1500
3	50%-74%	≥500 and <1000
4	≥75%	<500

1. Grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, fatal. Death occurring as a result of toxicity at any level of decrease from pretreatment will be reported as Grade 5.
2. Platelet counts must be below normal levels for Grades 1 to 4. If, at any level of decrease, the platelet count is $<20 \times 10^9$/L (20,000/μL), this will be considered Grade 4 toxicity, unless a severe or life-threatening decrease in the initial platelet count (eg, $<20 \times 10^9$/L [20,000/μL]) was present pretreatment, in which case the patient is not evaluable for toxicity referable to platelet counts.
3. Hemoglobin (Hb) levels must be below normal levels for Grades 1 to 4. Baseline and subsequent Hb determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity, but should be documented.
4. If the ANC reaches $<1 \times 10^9$/L (1000/μL), it should be judged to be Grade 3 toxicity. Other decreases in the white blood cell count, or in circulating neutrophils, are not to be considered because a decrease in the white blood cell count is a desired therapeutic endpoint. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was $<1 \times 10^9$/L (1000/μL) before therapy, the patient is not evaluable for toxicity referable to the ANC. The use of growth factors such as granulocyte colony-stimulating factor (G-CSF) is not relevant to the grading of toxicity, but should be documented.

Appendix D: Defining Prior and Concomitant Medication Flags

The figure below depicts various scenarios of prior and concomitant medications. The prior and concomitant medication flags are specified respectively for each scenario.



1 = start < first dose and stop < first doe
2 = start < first dose and stop >= first dose
3 =start >= first dose
4 = start > last dose + 30 days

Appendix E: Definition of Adverse Event of Special Interest and Events of Clinical Interest (MedDRA version 24.0)

1. Adverse Event of Special Interest (AESI)

The following preferred terms (PT) for the ventricular arrhythmias AESI include:

- Torsade de pointes
- Ventricular arrhythmia
- Ventricular extrasystoles
- Ventricular fibrillation
- Ventricular flutter
- Ventricular tachyarrhythmia
- Ventricular tachycardia

2. Events of Clinical Interest

The Events of Clinical Interest (ECIs) have been identified based on preclinical findings, emerging data from clinical studies relating to acalabrutinib, and pharmacological effects of approved Bruton's tyrosine kinase (BTK) inhibitors. The adverse events (AEs) selected for dedicated analysis were evaluated using Standardized MedDRA Queries (SMQs), where available, by System Organ Classes (SOCs), or by Sponsor-defined baskets of MedDRA Adverse Event Grouped Terms.

Category	Subcategory	Definition
Cardiac events		• SOC Cardiac disorders
	Atrial fibrillation	• PT Atrial fibrillation • PT Atrial flutter
	Ventricular tachyarrhythmias	• PT Torsade de pointes • PT Ventricular fibrillation • PT Ventricular flutter • PT Ventricular tachyarrhythmia • PT Ventricular tachycardia
Cytopenias – Anemia		• SMQ Haematopoietic erythropenia [narrow + broad]
Cytopenias – Leukopenia		• SMQ Haematopoietic leukopenia [narrow + broad]
	Neutropenia	• PT Band Neutrophil count decreased • PT Band neutrophil percentage decreased • PT Cyclic neutropenia • PT Febrile Neutropenia • PT Idiopathic neutropenia • PT Neutropenia • PT Neutropenic infection • PT Neutropenic sepsis

		• PT Neutrophil count decreased • PT Neutrophil percentage decreased
	Other leukopenia	• SMQ Haematopoietic leukopenia [narrow + broad] excluding PTs for neutropenia above
Cytopenias - Thrombocytopenia		• SMQ Haematopoietic thrombocytopenia [narrow + broad]
Hemorrhage		• SMQ Haemorrhage terms (excl laboratory terms)
	Major hemorrhage	• As per definition (see Section 3 below)
Hepatotoxicity		• SMQ [narrow] Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions • SMQ [narrow] Hepatitis, non-infectious • SMQ [narrow] Liver related investigations signs
Hypertension		• SMQ Hypertension [narrow]
Infections		• SOC Infections and infestations
Interstitial lung disease/Pneumonitis		• SMQ [narrow] Interstitial lung disease
Second primary malignancies		• SMQ Malignant tumours (including Haematological malignant tumours SMQ and Non-haemoatological malignant tumours SMQ) • SMQ Malignant lymphomas [narrow] SMQ Myelodysplastic syndrome [narrow]
	Second primary malignancies (excluding non melanoma skin)	• The above excluding PTs mapping to HLT Skin neoplasms malignant and unspecified (excluding melanoma)
Tumor lysis syndrome		• PT Tumour lysis syndrome

HLT=High-Level Term; PT=Preferred Term; SOC=System Organ Classes; SMQ=Standardized MedDRA Queries.

3. **Major Hemorrhage**

Major hemorrhage is defined as any hemorrhagic event that is serious, or Grade ≥ 3 in severity, or that is a CNS hemorrhage (any severity grade).

Search Strategy:

I. Use standardized MedDRA query:
   - Haemorrhage terms (excluding laboratory terms) (SMQ) [20000039]

II. Identify Major Events that are a subset of the Haemorrhage SMQ:
   - Grade ≥3 AE
   - Any serious adverse event
   - All grades of CNS hemorrhage

CNS Hemorrhage Preferred Terms

- Acute haemorrhagic leukoencephalitis
- Basal ganglia haematoma
- Basal ganglia haemorrhage
- Basilar artery perforation
- Brain contusion
- Brain stem haematoma
- Brain stem haemorrhage
- Brain stem microhaemorrhage
- Central nervous system haemorrhage
- Cerebellar haematoma
- Cerebellar haemorrhage
- Cerebellar microhaemorrhage
- Cerebral aneurysm perforation
- Cerebral aneurysm ruptured syphilitic
- Cerebral arteriovenous malformation haemorrhagic
- Cerebral artery perforation
- Cerebral cyst haemorrhage
- Cerebral haematoma
- Cerebral haemorrhage
- Cerebral haemorrhage foetal
- Cerebral microhaemorrhage
- Encephalitis haemorrhagic
- Epidural haemorrhage
- Extradural haematoma
- Haemorrhage intracranial
- Haemorrhagic cerebral infarction
- Haemorrhagic stroke

- Haemorrhagic transformation stroke
- Intracerebral haematoma evacuation
- Intracranial haematoma
- Intracranial tumour haemorrhage
- Intraventricular haemorrhage
- Meningorrhagia
- Ocular retrobulbar haemorrhage
- Optic disc haemorrhage
- Optic nerve sheath haemorrhage
- Pituitary haemorrhage
- Putamen haemorrhage
- Retinal aneurysm rupture
- Retinal haemorrhage
- Retinopathy haemorrhagic
- Ruptured cerebral aneurysm
- Spinal cord haematoma
- Spinal cord haemorrhage
- Spinal epidural haematoma
- Spinal epidural haemorrhage
- Spinal subarachnoid haemorrhage
- Spinal subdural haematoma
- Spinal subdural haemorrhage
- Subarachnoid haematoma
- Subarachnoid haemorrhage
- Subdural haematoma
- Subdural haematoma evacuation
- Subdural haemorrhage
- Subgaleal haematoma
- Subgaleal haemorrhage
- Subretinal haematoma
- Thalamus haemorrhage
- Traumatic intracranial haematoma

Traumatic intracranial haemo

Appendix F: – Search Strategy for Narratives

1. Primary Criteria for Narratives:

- All deaths (including due to progressive disease), other SAEs, AESIs (see Appendix 1 for definitions), AEs that led to discontinuation from study drug, pregnancies

2. Additional Criteria for Narratives:

- Subjects who fulfill ECI (see Appendix 1 for definitions) criteria and additional criteria for narratives as described below:

Note: the window for qualifying events for narratives is from first date of study drug to last date of study drug + 30 days. Beyond this window, narratives should also be provided for any related SAEs and for clinically significant AEs as judged by medical monitor.

ECI Category Name	ECI Subcategory Name	Additional Criteria for Narratives
Cardiac events	Atrial fibrillation	• Grade 3 and 4 PT Atrial fibrillation • Grade 3 and 4 PT Atrial flutter
Hemorrhage	Major hemorrhage	Same as ECI definition. Refer to Appendix 1 Section 2
Hepatotoxicity		Subjects who fulfill biochemical Hy's law criteria defined as below: $\geq$3×ULN AST or $\geq$3×ULN ALT and $\geq$2×ULN total bilirubin where bilirubin increased of ≥2xULN either coincides with ALT/AST elevations or follow them within 8 days
Second primary malignancies	Second primary malignancies (excluding non melanoma skin)	Below SMQs excluding PTs mapping to HLT Skin neoplasms malignant and unspecified (excluding melanoma) • SMQ Malignant tumours (including Haematological malignant tumours SMQ and Non- haemoatological malignant tumours SMQ • SMQ Malignant lymphomas [narrow] • SMQ Myelodysplastic syndrome [narrow]
Tumor lysis syndrome		Same as ECI definition. Refer to Appendix 1 Section 2

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; HLT=high-level term; ISS=integrated safety summary; PT=preferred term; SAE=serious adverse event; SMQ=Standardised MedDRA Query; ULN=upper limit of normal.
MedDRA version 24.0