Statistical Analysis Plan

Protocol Title: A Phase 2 Study of the Efficacy and Safety of ACP-196 in Subjects with Relapsed/Refractory CLL and Intolerant of Ibrutinib Therapy

Protocol Number: ACE-CL-208

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A Phase 2 Study of the Efficacy and Safety of ACP-196 in Subjects with Relapsed/Refractory CLL and Intolerant of Ibrutinib Therapy

Approval Page

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LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
ACP-196	acalabrutinib
AE(s)	adverse event(s)
ANC	absolute neutrophil count
ALC	absolute lymphocyte count
BID	twice per day
BOR	best overall response
BTK	Bruton tyrosine kinase
CBC	complete blood count
CI	confidence interval
CLL	chronic lymphocytic leukemia
CR	complete remission (response)
CRi	CR with incomplete bone marrow recovery
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DOL	duration of lymphocytosis
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
IPD	Important Protocol Deviation
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
CCI [redacted]	
NCI	National Cancer Institute
CCI [redacted]	
nPR	nodual partial remission
ORR	overall response rate
OS	overall survival
PFS	progression-free survival
PR	partial remission (response)
SAP	statistical analysis plan
TEAE(s)	treatment-emergent adverse event(s)
TTNT	time-to-next treatment
WHO	World Health Organization

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-208 Protocol Amendment 3.0 (dated 01 December 2017), which is entitled "A Phase 2 Study of the Efficacy and Safety of ACP-196 in Subjects with Relapsed/Refractory CLL and Intolerant of Ibrutinib Therapy."

If there are differences between protocol-specified analyses and the SAP, the SAP will supersede the protocol. Major differences will be noted, and rationale will be provided in Section 15.0 of this document.

2.0 STUDY OBJECTIVES

The primary objective is:

- Evaluate the efficacy of acalabrutinib in subjects with relapsed/refractory chronic lymphocytic leukemia (CLL) who are intolerant of ibrutinib therapy based on the modified International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 criteria.
    - The primary efficacy endpoint is overall response rate (ORR) assessed by the investigators.
    - The secondary efficacy endpoints are:
        - Duration of response (DOR)
        - Progression-free survival (PFS)
        - Time-to-next treatment (TTNT)
        - Overall survival (OS)

The secondary objective is:

- Evaluate the safety and tolerability of acalabrutinib in subjects with relapsed/refractory CLL who are intolerant of ibrutinib therapy
    - The safety endpoints are: Frequency, causal attribution, and severity of adverse events (AEs) based on the Common Terminology Criteria for Adverse Events (CTCAE v4.03) for both hematologic and nonhematologic AEs.
    - Frequency of AEs leading to discontinuation of study drug.

3.0 OVERALL STUDY DESIGN

This is a multicenter, open-label, Phase 2 study evaluating the efficacy and safety of acalabrutinib in subjects with relapsed/refractory CLL (N = 60) who are intolerant of ibrutinib therapy. For the purpose of this protocol, ibrutinib intolerant is defined as patients who cannot tolerate, or no longer can tolerate, ibrutinib therapy because of adverse reactions associated with treatment. Such patients may benefit from treatment with an alternative Bruton tyrosine kinase (BTK) inhibitor with a different safety profile than ibrutinib.

Subjects will be considered ibrutinib intolerant (at any dose/or duration) if they have discontinued ibrutinib therapy because of Grade 3 or 4 AEs that persisted in spite of optimal supportive care measures (e.g., atrial fibrillation/flutter, cardiac arrhythmia, diarrhea, rash, ecchymosis, myalgia, or arthralgia) or if subjects had Grade 2 AEs related to ibrutinib therapy, in spite of optimal supportive care measures, that persisted for ≥2 weeks or that recurred ≥2 times, whether dose was reduced or discontinued. Subjects will be treated with acalabrutinib 100 mg twice per day (BID). Treatment may be continued until disease progression or an unacceptable drug-related toxicity occurs.

For more details on study design, please refer to the protocol. Protocol amendments and revision dates are as follows:

- Original – 21 September 2015
- Amendment 1 – 14 January 2016
- Amendment 2 – 16 August 2016
- Amendment 3 – 01 December 2017
- Amendment 3.1 (France only) – 06 March 2018
- Amendments 4 and 4.1 (France only) – 24 Feb 2020

4.0 SAMPLE SIZE CONSIDERATION

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[redacted]

5.0 ANALYSIS POPULATIONS

Analysis populations will be defined in the following sections. The efficacy and safety analyses will be performed on the All-Treated Population.

5.1 Enrolled Population

The Enrolled Population will include all subjects who completed the enrollment procedures.

5.2 All-Treated Population

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

6.0 TREATMENTS AND MEDICATIONS

6.1 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.

6.2 Study Treatment Exposure

Study treatment exposure will be summarized for all subjects in the Safety Population.

The following will be provided for each treatment component when applicable:

- Duration of exposure
  - Acalabrutinib (months): (last dose date – first dose date + 1) / 30.4375
- Cumulative dose received on study (acalabrutinib)
- Average daily dose (acalabrutinib only)
  - Calculated as (total dose received [mg] / duration of exposure [days])
- Relative dose intensity
  - Acalabrutinib: Calculated as (total cumulative dose received [mg] / (duration of exposure [days] * 100 [mg] * 2) *100)

7.0 STATISTICAL METHODS

7.1 Data Presentation

No formal tests of hypotheses will be performed. 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.

7.2 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).

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

7.3 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 the Appendix.

7.4 Missing Data Handling

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

8.0 SUBJECT DISPOSITION

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

9.0 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.

10.0 DEMOGRAPHICS AND BASELINE DISEASE CHARACTERISTICS

The following variables collected at baseline will be presented:

- Demographics and baseline characteristics
  - 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)
  - Height
  - Weight

- ECOG performance status

➢ Baseline disease characteristics

- Time since initial CLL diagnosis to first dose (months)
- Rai stage – Rai stage collected on the electronic case report form (eCRF) and derived Rai stage based on variables collected at screening visit.
- Binet Stage
- Bulky disease (not applicable for Richter Syndrome/prolymphocytic leukemia) – defined as if at least one dimension of the lymph node measurement is
  - <5 cm
  - ≥5 cm
- B symptoms – weight loss, fever, night sweats
- Chromosomal abnormalities
  - del(17)(p13.1) (TP53)
  - del(11)(q22.3) (ATM)
  - Unmutated IGHV
- β2-microglobulin
  - >3.0 vs. ≤3.0 mg/L
- Number of prior systemic therapy
  - Descriptive statistics
  - <3 vs. ≥3
- Type of prior systemic therapy
- Time since most recent therapy (months)
- Cytopenia
  - Absolute neutrophil count (ANC) ≤1.5 x 10^9/L
  - Hemoglobin ≤11g/dL
  - Platelets ≤100 x 10^9/L
  - Hemoglobin ≤11g/dL or platelets ≤100 x 10^9/L
  - Any of the above
- Prior Transfusion with 28 days before treatment

- Autoimmune complication associated with CLL
- B symptoms
- ANC (10^9/L)
- Absolute lymphocyte count (ALC) (10^9/L)
- Hemoglobin (g/dL)
- Platelets (10^9/L)

11.0 MEDICAL HISTORY

Medical history will be summarized by system organ class (SOC) and preferred term (PT).

12.0 EFFICACY ANALYSIS

Response will be assessed by investigators based on IWCLL Response Assessment Criteria (modified from Hallek et al. 2008).

The efficacy analysis will be performed using All-Treated Population.

12.1 Primary Efficacy Endpoint and Analysis

12.1.1 Overall Response Rate

ORR is defined as the proportion of subjects achieving a best overall response (BOR) of either complete remission (CR), complete remission with incomplete bone marrow recovery (CRi), nodular partial remission (nPR), or partial remission (PR) at or before initiation of subsequent anticancer therapy. ORR will be analyzed per investigator's assessment.

ORR and the associated 95% exact (Clopper-Pearson) CI will be provided.

ORR will be summarized using All-Treated Population. Subgroup analysis for ORR will be peformed by chromosomal abnormalities.

The subgroup analysis of ORR will be performed for the following subgroups:

- del(17)(p13.1) - presence vs. absence
- del(11)(q22.3) - presence vs. absence
- del(17)(p13.1) and/or del(11)(q22.3)
- IGHV – unmutated vs. mutated
- TP53 – mutated vs. unmutated

12.2 Secondary Efficacy Endpoints and Analyses

12.2.1 Duration of Response

DOR is defined as the time from the date of achieving the first CR, CRi, nPR, 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 12.2.2.

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

12.2.2 Progression-Free Survival

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, whichever comes first. If a subject does not have disease progression or death, the data will be censored at the date of last adequate assessment (censoring date). 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 exam (PE) and complete blood count (CBC) or computed tomography (CT) 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	Date of Progression or Censoring	Outcome
PFS events include death or first disease progression that occurred at or prior to start of subsequent anticancer therapy, transplant, or the data analysis cutoff date.		
Death before first disease assessment	Date of death	Event
PD or death between scheduled assessments and before start of subsequent anticancer therapy	Earliest date of PD or death	Event
All other cases will be censored as follows:		
No adequate post-baseline assessment	Date of first dose	Censored
No PD or death before study exit	Date of last adequate disease assessment before data cutoff	Censored
No PD or death before start of subsequent anticancer therapy	Date of the last adequate disease assessment before start of subsequent anticancer therapy	Censored

No PD or death at the time of data cutoff (including subjects who had PD or died after cutoff)	Date of last adequate disease assessment before data cutoff	Censored

PD=progressive disease.

KM curve will be used to estimate the distribution of PFS. Median PFS and the 95% CIs and PFS rates for selected landmarks with 95% CIs will be reported. Number of progressions, deaths, and censored events by reason will be summarized.

12.2.3 Time-to-Next Treatment

TTNT is defined as the time from date of first acalabrutinib treatment to date of institution of subsequent anticancer therapy for CLL or death due to any cause, whichever comes first. Subjects who do not have the above specified events prior to the data cutoff date will be censored at the date of last visit. TTNT will be calculated as follows:

(Earlier date of institution of subsequent anticancer therapy for CLL or date of death due to any cause) – date of first dose + 1. For censored subjects, date of last visit will replace earlier date of use of subsequent anticancer therapy for CLL or date of death due to any cause in the calculation.

12.2.4 Overall Survival

OS is defined as the time from date of first dose date to date of death due to any cause. Subjects who did not have a confirmed death at or prior to the analysis data cutoff date will be censored as following:

Situation	**Date of Censoring**
Lost to follow-up immediately after first dose	First dose date
No confirmed death at or prior to analysis data cutoff date	Date last known to be alive before analysis data cutoff date

OS will be calculated as death date (or censoring date) – first dose date + 1.

13.0 SAFETY ENDPOINTS

Safety analyses will be performed using the All-Treated Population unless specified otherwise.

Safety will be assessed by evaluation of treatment-emergent adverse events, laboratory values (hematology, clinical chemistry, urinalysis, and other laboratory variables), vital signs, electrocardiogram (ECG) results, physical exams, and Eastern Cooperative Oncology Group (ECOG) performance status.

13.1 Adverse Events

AEs will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA) reporting system at the time of the database lock. The investigator will grade AEs according to the National Cancer Institute (NCI) CTCAE v4.03 for AEs. Hematologic toxicity is assessed by the grading scale in the IWCLL 2008. Treatment-emergent AEs (TEAEs) 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 AEs will be presented by System Organ Class (SOC) and preferred term (PT). If a subject experiences the same event more than once, the event will be counted only once under the maximum severity (in tabulation). AEs will be presented by relationship and by severity. The investigator will judge each event to be "not related" or "related" to study treatment.

Summaries will be presented for:

- TEAEs
- Treatment-emergent serious adverse events
- Treatment-related adverse event
- Treatment-related serious adverse events
- Grade ≥3 TEAEs
- Grade ≥3 treatment-related TEAEs
- Grade 5 TEAEs
- AEs that led to study drug discontinuation, dose modifications, or dose delay
- Listings of TEAEs, serious AEs, TEAEs that led to study drug discontinuation, and death will be provided
- Events of Clinical Interest defined in the version available at the time of database lock

13.2 Laboratory Assessments

13.2.1 Hematology, Chemistry, and Immunology Parameters

All laboratory values will be converted to and reported as International System of Units (SI units) and classified as normal, low, or high based on the normal ranges provided by the central laboratory. In general, only data from the central laboratory (samples from local laboratories can be used if central laboratory testing is unavailable) will be summarized and analyzed.

Hematologic parameters including platelet counts, hemoglobin, and neutrophils will be assessed by the grading scale for hematologic toxicity in CLL studies in the IWCLL 2008 guidelines and NCI CTCAE v4.03. All other gradable laboratory parameters will be graded using the NCI CTCAE v4.03.

Per the grading scale in the IWCLL guidelines, (1) ANC: Both baseline grade and post-baseline grade are defined based on absolute values and (2) Hemoglobin and platelet:

baseline grade is not applicable (no criterion is provided to define baseline grade) and post-baseline grade is based on percent decrease from baseline value.

Gradable parameters that have criteria available for both low and high values (e.g., hypercalcemia for a high value of calcium and hypocalcemia for a low value of calcium) based on the NCI CTCAE v4.03 will be summarized for both criteria (low and high). Subjects will only be counted once for each criterion/direction. The same subject can be counted for both criteria if the subject has laboratory values meeting each criterion. Subjects meeting the criteria for Grade 1 or higher for the high direction will be summarized under Grade 0 when summarizing the low direction and vice versa.

For each laboratory parameter, the baseline laboratory value/grade is defined as the last laboratory value/grade collected on or prior to the date of the first dose of study drug. The change from baseline to post-baseline value will be calculated for each parameter.

13.2.2 CCI

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13.2.3 Serum Immunoglobulin

For serum immunoglobulin (IgG, IgM, and IgA) levels, descriptive statistics or figure over time will be presented.

13.2.4 Analysis of Lymphocytosis

For all subjects with baseline and any post-baseline ALC measurements, ALC at peak summary will be provided by treatment arm. Median percent change in ALC from baseline along with its 95% CI will also be displayed graphically overall time.

Lymphocytosis is defined as an elevation in ALC of ≥50% compared to baseline and a post-baseline assessment >5,000/µL or a post-baseline assessment ≥400,000/µL (the latter definition is an exploratory endpoint for the study). The number of subjects with at least one occurrence of lymphocytosis will be summarized. For subjects with lymphocytosis, resolution of lymphocytosis is defined as 1) a decrease of ALC value to the baseline level or lower, or 2) an achievement of ALC value that is below 5,000/µL, whichever occurs first.

The following analyses will be conducted for subjects with lymphocytosis by treatment arm:

- ALC at peak and time to peak ALC for subjects who have lymphocytosis will be summarized with descriptive statistics.
- Duration of lymphocytosis (DOL) is defined as the duration of time from the earliest date on which the ALC value met the lymphocytosis criteria at a post-baseline assessment to the earliest date on which a subsequent ALC value met the resolution criteria.
    - DOL = Earliest date of meeting resolution criteria - Earliest date of meeting lymphocytosis criteria + 1.

Confirmation is not required for resolution of lymphocytosis. Subjects who developed lymphocytosis but whose lymphocytosis was not resolved prior to the analysis cutoff date will be censored at the last sample date with non-missing ALC value at or prior to the analysis cutoff date. KM curves will be used to estimate the distribution of DOL. The 50th percentile of KM estimates along with its two-sided 95% CI will be used to estimate the median DOL.

13.3 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.

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

13.4 ECOG Performance Status

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

14.0 CCI [redacted]

CCI [redacted]

15.0 DEVIATIONS FROM STATISTICAL PLAN IN PROTOCOL AND OTHER ISSUES

Given the scope of the planned CSR for this study, Efficacy-Evaluable Population will not be derived, and sensitivity analyses will not be performed.

CCI [redacted]

16.0 REFERENCES

Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood 2008;111:5446–56.

17.0 APPENDIX

Appendix: Analysis Windows

Tumor Assessment/CT				
			Analysis Window (Study Day)	
Nominal Visit	Study Day	Nominal Month	Lower (inclusive)	Upper (inclusive)
C1D1	1	0		1
C1D15	15	1	2	8
C1D28	28	1	9	22
C2D15	43	2	23	36
C2D28	56	2	37	50
C3D28	84	3	51	70
C4D28	112	4	71	98
C5D28	140	5	99	126
C6D28	168	6	127	154
C9D28	252	9	155	210
C12D28	336	12	211	294
C15D28	420	15	295	378
C18D28	504	18	379	462
C21D28	588	21	463	546
C27D28	756	27	547	672
C33D28	924	33	673	840
C39D28	1092	39	841	1008
C45D28	1260	45	1009	

C=Cycle; CT=computed tomography; D=Day.

Hematology / Chemistry				
			Analysis Window (Study Day)	
Nominal Visit	**Study Day**	**Nominal Month**	**Lower** (inclusive)	**Upper** (inclusive)
Screening	1	0		1
C1D15	15	1	2	8
C1D28	28	1	9	22
C2D15	43	2	23	36
C2D28	56	2	37	50
C3D28	84	3	51	70
C4D28	112	4	71	98
C5D28	140	5	99	126
C6D28	168	6	127	154
C9D28	252	9	155	210
C12D28	336	12	211	294
C15D28	420	15	295	378
C18D28	504	18	379	462
C21D28	588	21	463	546
C24D28	672	24	547	630
C27D28	756	27	631	714
C30D28	840	30	715	798
C33D28	924	33	799	882
C36D28	1008	36	883	966
C39D28	1092	39	967	1050
C42D28	1176	42	1051	

C=Cycle; D=Day.
Note: No C1D1 data. Only screening available.

Vital Signs / Physical Examination / ECOG				
			Analysis Window (Study Day)	
Nominal Visit	**Study Day**	**Nominal Month**	**Lower** (inclusive)	**Upper** (inclusive)
C1D1	1	0		1
C1D15	15	1	2	8
C1D28	28	1	9	22
C2D15	43	2	23	36
C2D28	56	2	37	50
C3D28	84	3	51	70
C4D28	112	4	71	98
C5D28	140	5	99	126
C6D28	168	6	127	154
C9D28	252	9	155	210
C12D28	336	12	211	294
C15D28	420	15	295	378
C18D28	504	18	379	462
C21D28	588	21	463	546
C24D28	672	24	547	630
C27D28	756	27	631	714
C30D28	840	30	715	798
C33D28	924	33	799	882
C36D28	1008	36	883	966
C39D28	1092	39	967	1050
C42D28	1176	42	1051	

C=Cycle; Day=Day; ECOG=Eastern Cooperative Oncology Group.