Statistical Analysis Plan

A Phase 1/2 Proof-of-Concept Study of the Combination of ACP-196 and ACP-319 in Subjects with B-cell Malignancies

Protocol Number: ACE-LY-001

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TABLE OF ABBREVIATIONS

AE(s)	adverse event(s)
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BTK	Bruton tyrosine kinase
CI	confidence interval
CLL	chronic lymphocytic leukemia
CNS	central nervous system
CR	complete response
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
DOR	duration of response
ECG	Electrocardiogram
ECI(s)	events of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
HT	high-level term
IPD	important protocol deviation
ISS	integrated safety summary
KM	Kaplan-Meier
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NCI	National Cancer Institute
ORR	overall response rate
PD	progressive disease
PD	pharmacodynamics
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
PRL	partial response with treatment-induced lymphocytosis
PT	preferred term
SAE(s)	serious adverse event(s)

SAP	statistical analysis plan
SD	stable disease
SLL	small lymphocytic lymphoma
SMQs	standardized MeDRA Queries
SOC	system organ class
TEAE(s)	treatment-emergent adverse events
ULN	upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the planned statistical analyses for clinical study report that have been outlined within Protocol Amendment 5 for Study ACE-LY-001, which is entitled “A Phase 1/2 Proof-of-Concept Study of the Combination of ACP-196 and ACP-319 in Subjects with B-cell Malignancies” dated 11 December 2018. Hereafter, acalabrutinib (a generic name for ACP-196) will be used in place of ACP-196 in this document.

2. OBJECTIVES

2.1 Primary Objectives

- To characterize the safety profile of acalabrutinib and ACP-319 in subjects with relapsed or refractory B-cell malignancies.

2.2 Secondary Objectives

- To document the extent of study drug exposure as determined by coadministration of acalabrutinib and ACP-319
- To evaluate the pharmacodynamics (PD) effects of acalabrutinib and ACP-319 administration
- To evaluate the activity of acalabrutinib and ACP-319 as measured by response rate, duration of response, progression-free survival, and time-to-next treatment

3. STUDY OVERVIEW

3.1 Study Design

This study is a multicenter, open-label, nonrandomized, sequential group, dose-escalation study to be conducted at approximately 30 sites. The study is divided into 2 parts: Part 1 of the study is the dose-escalation portion and Part 2 allows for possible expansion groups. Detailed study design can be found in protocol Section 3.0. Starting with protocol Amendment 3, subjects with CLL/SLL will receive acalabrutinib monotherapy (100 mg BID), as CCI

Refer to protocol Appendix 6 and Appendix 7 for a comprehensive list of study assessments and their timing.

3.2 Sample Size

CCI

CCI

CCI

CCI

CCI

4. STUDY ENDPOINTS

4.1 Safety Endpoints

The safety of acalabrutinib and ACP-319 will be characterized by the type, frequency, severity, timing of onset, duration, and relationship to study drug(s) of any treatment-emergent adverse events (AEs) or abnormalities of laboratory tests; serious adverse event (SAEs); or AEs leading to discontinuation or dose reduction of study treatment.

4.2 Efficacy Endpoints

- Overall Response rate (ORR)
- Duration of response (DOR)

- Progression-free survival (PFS)
- Time-to-next treatment

4.3 Pharmacokinetic (PK) and Pharmacodynamic (PD) Parameters

PK and PD analyses will be performed and reported in a separate report.

5. ANALYSIS SETS

5.1 All-treated Population

The safety analyses and primary efficacy analyses will be performed on the All-treated population, defined as all enrolled subjects who receive ≥1 dose of any study drug.

5.2 Efficacy-evaluable Population

Efficacy-evaluable population: All subjects in the All-treated population who have ≥ 1 evaluable response assessment after the first dose of study drug. Sensitivity analyses for efficacy will be carried out on the Efficacy-evaluable population.

6. MISSING VALUES

No imputation of values for missing data will be performed except that missing or partial start and end dates for AEs and concomitant medication will be imputed according to prespecified, conservative imputation rules. Subjects lost to follow-up will be included in statistical analyses to the point of their last evaluation.

Imputation of partial dates will be made for AE onset and stop dates, start and end dates of concomitant medication, start date of subsequent anticancer therapy, date of initial diagnosis and death date. If dates are completely missing, no imputation will be made. For any partial date with missing year, no imputation will be made.

The general rule for imputation is:

- If only day is missing, then the 15th of the month will be used.
- If only year is present, then June 30th will be used.

If such imputation date for initial diagnosis is on or after date of first dose, the date of first dose – 1 will be used. If such imputed date for subsequent anticancer therapies is before date of last dose, the date of last dose + 1 will be used.

If the imputed date is for an AE start date and is in the same year and month as the first dose date but before the first dose date, then the first dose date will be used, or if the imputed AE

start date is after the AE end date, then the AE end date will be used. If the imputed date is for an AE start date and is in the same year and month as but after the last dose date + 30 days, then the last dose date + 30 days will be used.

If the imputed date is for an AE end date and is after the death date, the date of death will be used, or if the imputed AE end date is before the AE start date, the AE start date will be used.

7. STATISTICAL METHODS OF ANALYSIS

7.1 General Principles

Descriptive statistics will be used to summarize baseline demographic and disease characteristics, study drug administration, efficacy and safety outcomes. Descriptive summaries of discrete data will present the sample size and the incidence as a frequency and as a percentage. Descriptive summaries of continuous data will present the sample size, group mean, standard deviation (SD), median, and range. Confidence intervals (CIs) may be included as appropriate.

Baseline data, subject accountabilities, treatment, medications and safety analysis will be summarized by cohorts for Part 1, by DLBCL histologies (GCB DLBCL & NON-GCB DLBCL from both Part 1 and Part 2) as well as by disease histology subtype (CLL/SLL, MCL, WM, and FL) within All- treated population. Primary efficacy analysis Response Rate will be summarized by histologies for Part 1 and by DLBCL histologies (GCB DLBCL & NON-GCB DLBCL from both Part 1 and Part 2) within All- treated population, while the rest of efficacy analysis including Duration of Responses, Progression Free Survival and Time to Next Treatment will be summarized by DLBCL histologies (GCB DLBCL & NON-GCB DLBCL from both Part 1 and Part 2) within All- treated population only.

7.2 Subject Accountability

Subject disposition will be summarized for All- treated Subjects including the following information:

- Subject status on study drug
- Count and reason for study drug discontinuation
- Subject status on study
- Count and reason for study termination
- Time on study

7.3 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 of IPDs table and the List of Subjects with IPDs.

7.4 Baseline Data

Summaries of demographics and baseline characteristics will be presented for subjects in the All- treated population.

7.4.1 Demographics

- Sex (Male, Female)
- Age (continuous)
- Age category (≥ 65 years)
- Ethnicity
- Race

7.4.2 Baseline Characteristics

- Height (cm)
- Weight (kg)
- ECOG performance status at baseline

7.4.3 Baseline Disease Characteristics

- Prior Number of Regimens
- Tumor bulk (grouped as <5 cm, ≥5 and <10 cm, ≥10 cm)
- B Symptoms
- Rai Staging
- Ann Arbor Staging for lymphoma

Baseline disease characteristics will be summarized by disease histologies within All- treated population. The baseline disease characteristics applicable to each disease histology are summarized in below Table 2:

Table 2. Baseline Disease Characteristics by Disease Histology

	CLL/SLL	MCL	WM	FL	GCB DLBCL	NON-GCB DLBCL
Prior Number of Regimens	x	x	x	x	x	x
Tumor bulk	x	x	x	x	x	x
B Symptoms	x	x	x	x	x	x
Rai Staging	x					
Ann Arbor Staging for Lymphoma		x		x	x	x

7.5 Treatment and Medications

7.5.1 Prior and Concomitant Medications and Therapy

Prior medications/therapies are defined as medications with a start date occurring before the date of first dose of study treatment. Concomitant medications/therapies are defined as medications that: Had start date between the first dose date of study drug, 30 days (+7) after the last dose of study drug, or the first dose date of new anticancer therapy, whichever is earlier, or had start date before first dose date and stopped or continued after first dose date. In addition, medications/therapies that meet the criteria for both prior and concomitant medications will be classified as both prior and concomitant medication/therapies. Start date and end date will be imputed based on the rules provided in Section 6 of the SAP. Medications with completely missing start and stop dates will be considered as concomitant medications.
Prior and concomitant medications will be summarized by the World Health Organization (WHO) Drug Dictionary therapeutic class, pharmacological class, and preferred term.

7.5.2 Exposure to Study Drug

Descriptive statistics (n, mean, standard deviation, median, and range) will be used to summarize the following regarding acalabrutinib and ACP-319 exposure:

- The number of subjects who received at least one dose of acalabrutinib and ACP-319
- Duration of exposure (the interval between first dose date and last dose date)
  - The number of cycles that subjects received both drugs
- Actual cumulative dose (the total dose administered during the drug exposure period)
- Average daily dose (the ratio of total dose administered and treatment duration)

- Relative dose intensities (the ratio of average daily dose and prescribed doses)

Dose withholding is defined as missing dose for ≥ 7 consecutive days. Dose reduction of acalabrutinib is defined as taking lower dose level (100 mg QD) for ≥ 3 consecutive days. Dose reduction of ACP-319 in Part 2 is defined as taking lower dose level (25 mg BID or 25 mg QD) ≥ 3 consecutive days. Number of subjects with dose withholding and dose reduction will be summarized.

7.6 Analyses of Efficacy Endpoints

7.6.1 Response Rate

ORR is defined as the proportion of subjects who achieve a response of partial response (PR) or complete response (CR) per investigator's assessment to treatment. See Section 4.2 in the protocol for details about the criteria investigator uses for each disease histology.

The primary analysis of ORR will be conducted on the all-treated population. ORR and the corresponding 95% two-sided CI calculated using exact binomial distribution will be presented. The order of overall response category is CR > PR > SD > PD. For best overall response, each subject will be classified to only one response category based on subject's the best response during the study. Descriptive statistics will be provided for best overall response. The number and proportion of subjects within each category of response as well as the associated 95% CIs will be presented. The proportion will be estimated by dividing the number of subjects within each category of response by the total number of subjects in the analysis population.

7.6.2 Duration of Response

The duration of overall response (DOR) is defined as the interval from the first documentation of response (CR or PR) to the earlier of the first documentation of definitive disease progression or death from any cause. Data from surviving, non-progressing subjects will be censored at the earliest of the time of initiation of anticancer treatment other than the study treatment or the last time that lack of disease progression was objectively documented. The censoring rules for DOR are summarized in Appendix10.2. The DOR will be estimated using the Kaplan-Meier (KM) method. KM estimates with 95% CIs will be calculated for event time quartiles, and event-free rates will be calculated at selected time points. In addition, the reason for censoring will be summarized.

7.6.3 Progression-free Survival

Progression-free survival is defined as the interval from the start of acalabrutinib and ACP-319 therapy to the earlier of the first documentation of objective disease progression or death from any cause. Data from surviving, non-progressing subjects will be censored at the earliest of the time of initiation of anticancer treatment other than the study treatment or the last time that lack of disease progression was objectively documented. The censoring rules for PFS analysis are summarized Appendix10.3. PFS will be analyzed using the same method as that for DOR.

7.6.4 Time to Next Treatment

Time-to-next treatment defined as the time from start of acalabrutinib and ACP-319 therapy on this protocol to the start of subsequent anticancer therapy. Data from subjects who have not received subsequent therapy will be censored at the earliest of death or the last time that lack of administration of a new therapy was objectively documented. Time-to-next treatment will be analyzed using the same method as that for DOR.

7.7 Analyses Safety Endpoints

Safety analyses will be performed on the All-treated Population.

7.7.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs to a system organ class and a preferred term. The severity of the AE will be assessed by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 or higher. Drug-related AEs are those assessed by investigator as related.

Treatment-emergent adverse events (TEAEs) are defined as those events that occur (actual or imputed start date) on or after the first dose of study drug, through the treatment phase, and within 30 days following the last dose of study drug.

Treatment-emergent AEs will be summarized by system organ class and preferred terms in descending order of frequency, by NCI toxicity grade and by relationship to study drug. The same summary will be provided for serious treatment-emergent AEs and drug-related serious treatment-emergent AEs, treatment-emergent AEs leading to treatment discontinuation, dose reductions and dose withheld.

Death information is reported in the study exit CRF for all deaths. Incidences of deaths are to be reported, along with the primary cause of death.

7.7.2 Adverse Events of Clinical Interest

In addition to general analyses of adverse events, events of clinical interest (ECIs) will be summarized by frequency and by CTCAE toxicity grade.

The definitions of ECI categories are presented in Appendix10.4.

7.7.3 Laboratory Test Results

Laboratory data of hematology, serum chemistry up to 30 days after last dose or the safety follow-up visit date, whichever is later, will be reported in SI units. Applicable laboratory results will be graded according to CTCAE Version 4.03 or higher. Generic normal ranges will be applied whenever reference ranges are not available.

Shift from baseline to the worst grade during the treatment will be provided as shift tables for selected parameters. Figures of changes in selected parameters will be plotted overtime as appropriate.

Urinalysis data will be summarized as appropriate.

7.7.4 Vital Signs

Summary statistics (mean, standard deviation, median, and range) will be produced for vital signs at baseline, maximum, change from baseline to maximum, last value, and change from baseline to last value.

In order to be included in the table, a subject must have both a baseline value and a value for the given post-baseline time point.

7.7.5 ECOG Performance Status

Change of Eastern Cooperative Oncology Group (ECOG) performance status from baseline to the worst score during the treatment will be provided as shift tables.

7.7.6 Physical Examinations

Physical examination data collected at screening and post-treatment will be summarized. Descriptive statistics will be calculated for each parameter.

8 CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

There is no major change from protocol-specified analyses.

9 LITERATURE CITATIONS I REFERENCES

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FDA Drug Safety Communication 2012. Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies (December 2012). Available at: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM227351.pdf, accessed on: 13May2017.

10 APPENDICES

10.1 Study day

The study day will be calculated in reference to the date of first dose date. Study Day 1 is defined as the date of first dose of any study drug. For assessments that occur on or after first dose date, study day is defined as (date of assessment – date of first dose + 1). For assessments that occur prior to first dose date, study day is defined as (date of assessment – date of first dose). There is no Study Day 0.

10.2 Censoring Rules for Duration of Response

Situation	Outcome	Date	Event Description/ Censoring Reason
Progression documented between scheduled visits on or before receiving subsequent anticancer therapy or data cutoff, whichever occurred first	Event	Earliest date of disease assessment documenting progression	PD
Death without documented PD and not receiving subsequent anticancer therapy on or before data cutoff	Event	Date of Death	Death
Documented PD or death after subsequent anticancer therapy and the subsequent anticancer started before data cutoff date	Censored	Date of last adequate disease assessment prior to subsequent anticancer treatment	Subsequent anticancer therapy
No documented PD or death at the time of data cutoff and subsequent anticancer therapy started before the data cutoff	Censored	Date of last adequate disease assessment prior to subsequent anticancer treatment	Subsequent anticancer therapy
Documented PD or death after subsequent anticancer therapy and the subsequent anticancer started after data cutoff date	Censored	Date of last adequate disease assessment on or before data cutoff	Data cutoff
No documented PD or death at the time of data cutoff and subject not received subsequent anticancer therapy or subsequent anticancer therapy started after the data cutoff	Censored	Date of last adequate disease assessment on or before data cutoff	Data cutoff
Withdrew consent before documented PD or death	Censored	Date of last adequate disease assessment	Withdrew consent
Lost to follow-up before documented PD or death	Censored	Date of last adequate disease assessment	Lost to follow-up

10.3 Censoring Rules for Progression-free Survival

Situation	Outcome	Date	Event Description/ Censoring Reason
Progression documented between scheduled visits on or before receiving subsequent anticancer therapy or data cutoff, whichever occurred first	Event	Earliest date of disease assessment documenting progression	PD
Death without documented PD and not receiving subsequent anticancer therapy on or before data cutoff	Event	Date of Death	Death
Death occurred prior to first disease assessment	Event	Date of Death	Death
Documented PD or death after subsequent anticancer therapy and the subsequent anticancer started before data cutoff date	Censored	Date of last adequate disease assessment prior to subsequent anticancer treatment	Subsequent anticancer therapy
No documented PD or death at the time of data cutoff and subsequent anticancer therapy started before the data cutoff	Censored	Date of last adequate disease assessment prior to subsequent anticancer treatment	Subsequent anticancer therapy
Documented PD or death after subsequent anticancer therapy and the subsequent anticancer started after data cutoff date	Censored	Date of last adequate disease assessment on or before data cutoff	Data cutoff
No documented PD or death at the time of data cutoff and subject not received subsequent anticancer therapy or subsequent anticancer therapy started after the data cutoff	Censored	Date of last adequate disease assessment on or before data cutoff	Data cutoff
Withdrew consent without documented PD or death	Censored	Date of last adequate disease assessment	Withdrew consent
Lost to follow-up without documented PD or death	Censored	Date of last adequate disease assessment	Lost to follow-up
No post-baseline adequate disease assessments	Censored	Date of first dose	No post-baseline adequate disease assessments
No baseline disease assessments	Censored	Date of first dose	No baseline disease assessment

10.4 Search Strategy for Events of Clinical Interest

1. Events of Clinical Interest

The Events of Clinical Interest (ECIs) have been identified based on nonclinical findings, emerging data from clinical studies relating to acalabrutinib, and pharmacological effects of approved BTK inhibitors. The AEs selected for dedicated analysis were evaluated using Standardized MedDRA Queries (SMQs), where available, by system organ class (SOC), or by sponsor-defined baskets of MedDRA Adverse Event Grouped Terms.

Category Name	Subcategory Name	Definition
Cardiac events		x SOC Cardiac disorders
	Atrial fibrillation	x PT Atrial fibrillation x PT Atrial flutter
	Ventricular tachyarrhythmias	x PT Ventricular fibrillation x PT Ventricular flutter x PT Torsade de pointes x PT Ventricular tachyarrhythmia x PT Ventricular tachycardia
Cytopenias – Anemia		x SMQ Haematopoietic erythropenia [narrow + broad]
Cytopenias – Leukopenia		x SMQ Haematopoietic leukopenia [narrow + broad]
	Neutropenia	x PT Febrile Neutropenia x PT Neutropenia x PT Neutropenic infection x PT Neutropenic sepsis x PT Neutrophil count decreased x PT Neutrophil percentage decreased x Neutropenia neonatal x Idiopathic neutropenia x Band Neutrophil count decreased x Band neutrophil percentage decreased
	Other Leukopenia	x SMQ Haematopoietic leukopenia [narrow + broad] excluding PTs for neutropenia above
Cytopenias - Thrombocytopenia		x SMQ Haematopoietic thrombocytopenia [narrow + broad]
Hemorrhage		x SMQ Haemorrhage terms (excl laboratory terms)
	Major hemorrhage	x As per Acerta definition (Appendix 2 Section 4)
Hepatotoxicity		x SMQ [narrow] Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions x SMQ [narrow] Liver related investigations signs

Category Name	Subcategory Name	Definition
		x SMQ [narrow] Hepatitis, non-infectious
Hypertension		x SMQ Hypertension [narrow]
Infections		x SOC Infections and infestations
Interstitial lung disease/Pneumonitis		x SMQ [narrow] Interstitial lung disease
Second primary malignancies		x SMQ Malignant tumors (including Haematological malignant tumors SMQ and Non-haemoatological malignant tumors SMQ x SMQ Malignant lymphomas [narrow] x SMQ Myelodysplastic syndrome [narrow]
	Second primary malignancies (excluding non-melanoma skin)	x The above excluding PTs mapping to HLT Skin neoplasms malignant and unspecified (excl melanoma)
Tumor lysis syndrome		x PT Tumor lysis syndrome

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=Standardized MedDRA Query; SOC=system organ class; ULN=upper limit of normal.
MedDRA version 21.1
"No additional criteria" means only SAE, AE that led to study drug discontinuation, and deaths within specified window will be selected for narratives.
"Any" means any subject with a PT in the category will be selected for narratives.

2. Major Hemorrhage

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

SearchStrategy:

I. Use standardized MedDRA v21.1 Query:
   - Haemorrhage terms (excl laboratory terms) (SMQ) [20000039]

II. Identify Major Events that are a subset of the Haemorrhage SMQ:
   - Grade ≥ 3 AE
   - Any SAE
   - All Grades of CNS hemorrhage

CNS Hemorrhage Preferred Terms (MedDRA v21.1):

Acute haemorrhagic leukoencephalitis	Intracerebral haematoma evacuation
Basal ganglia haematoma	Intracranial haematoma
Basal ganglia haemorrhage	Intracranial tumour haemorrhage
Basilar artery perforation	Intraventricular haemorrhage
Brain contusion	Intraventricular haemorrhage neonatal

Brain stem haematoma	Meningorrhagia
Brain stem haemorrhage	Ocular retrobulbar haemorrhage
Brain stem microhaemorrhage	Optic disc haemorrhage
Central nervous system haemorrhage	Optic nerve sheath haemorrhage
Cerebellar haematoma	Periventricular haemorrhage neonatal
Cerebellar haemorrhage	Pituitary haemorrhage
Cerebellar microhaemorrhage	Putamen haemorrhage
Cerebral aneurysm perforation	Ruptured cerebral aneurysm
Cerebral aneurysm ruptured syphilitic	Spinal cord haematoma
Cerebral arteriovenous malformation haemorrhagic	Spinal cord haemorrhage
Cerebral artery perforation	Spinal epidural haematoma
Cerebral haematoma	Spinal epidural haemorrhage
Cerebral haemorrhage	Spinal subarachnoid haemorrhage
Cerebral haemorrhage foetal	Spinal subdural haematoma
Cerebral haemorrhage neonatal	Spinal subdural haemorrhage
Cerebral microhaemorrhage	Subarachnoid haematoma
Encephalitis haemorrhagic	Subarachnoid haemorrhage
Epidural haemorrhage	Subarachnoid haemorrhage neonatal
Extradural haematoma	Subdural haematoma
Haemorrhage intracranial	Subdural haematoma evacuation
Haemorrhagic cerebral infarction	Subdural haemorrhage
Haemorrhagic stroke	Subgaleal haematoma
Retinal aneurism rupture	Subgaleal haemorrhage
Retinal haemorrhage	Thalamus haemorrhage
Subretinal haematoma	Traumatic intracranial haemorrhage
Haemorrhagic transformation stroke	Traumatic intracranial haematoma