Protocol Number: ACE-MY-001

Protocol Title: An Open-label, Phase 1b Study of ACP-196 in Subjects with Multiple Myeloma

Version: 2.0

Version date: 20 September 2018

The undersigned have reviewed this plan and find it to be consistent with the requirements of the protocol as it applies to their respective areas

Prepared by

[redacted] Associate Director, Biostatistics

[redacted]

Statistical Analysis Plan

An Open-label, Phase 1b Study of ACP-196 in Subjects with Multiple Myeloma

Protocol Number: ACE-MY-001

Version:	**Version 2.0**
Date:	**20 September, 2018**
Study Statistician:	[redacted]

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TABLE OF ABBREVIATIONS

AE(s)	adverse event(s)
Bid	twice per day
CBR	clinical benefit rate
CR	complete response
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
Ex-US	Excluding United States of America
Ig	immunoglobulin
IRC	independent review committee
IPD	important protocol deviation
ISS	International Staging System
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
MR	minimal response
NCI	National Cancer Institute
PD	pharmacodynamics
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
PT	preferred term
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
sCR	stringent complete response
SD	stable disease
TEAE(s)	treatment-emergent adverse events
VGPR	very good partial response
WHO	World Health Organization

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide details of the safety and efficacy analyses that have been outlined within Protocol Amendment 2 for Study ACE-MY-001, which is entitled "An Open-label, Phase 1b Study of ACP-196 in Subjects with Multiple Myeloma" dated January 13, 2016. The original SAP based on same protocol was for interim safety clinical study report (CSR) to support the new drug application (NDA) in relapsed and refractory mantle cell lymphoma. This SAP is updated to include efficacy analysis. Any change to the planned analyses described in the final SAP will be documented in the clinical study report (CSR).

Separate reports will be generated for pharmacokinetic (PK) and pharmacodynamic (PD) data.

From here on, acalabrutinib (generic name for formerly ACP-196) will be used in place of ACP-196 in this document.

2. OBJECTIVES

2.1 Primary Objective

- To characterize the safety profile of acalabrutinib with and without dexamethasone in subjects with relapsed or refractory (R/R) multiple myeloma (MM).

2.2 Secondary Objectives

- To characterize the PK profile of acalabrutinib with and without dexamethasone and the PK profile of dexamethasone with concomitant acalabrutinib administration
- To evaluate the PD effects of acalabrutinib with and without dexamethasone
- To evaluate the activity of acalabrutinib with and without dexamethasone as measured by overall response rate (ORR), duration of response (DOR), clinical benefit rate, disease control rate, and progression-free survival (PFS).
- To explore the relationship between biological markers in MM cells and response to therapy

3. STUDY OVERVIEW

3.1 Study Design

This study is a multicenter, open-label, randomized, parallel-group study to be conducted at approximately 20 sites in 2 countries (United Kingdom and United States). Forty subjects are planned to be randomized 1:1 into the following 2 cohorts to receive acalabrutinib, with or without dexamethasone:

- Cohort 1 (acalabrutinib monotherapy): acalabrutinib 100 mg bid continuously
- Cohort 2 (acalabrutinib + dexamethasone): acalabrutinib 100 mg bid continuously and 40 mg dexamethasone once weekly

Due to limited evidence of efficacy of acalabrutinib monotherapy in R/R MM subjects in this study, in a memo dated March 15, 2016 to all study sites, the enrollment was discontinued immediately and subjects who were randomized to receive acalabrutinib monotherapy were permitted to crossover to receive acalabrutinib + dexamethasone treatment.

One cycle is defined as a 28-day study treatment period. Treatment may be continued until disease progression (PD) or an unacceptable drug-related toxicity occurs. All subjects who discontinue study drug will have a safety follow-up visit 30 (±7) days after the last dose of study drug unless they have started another cancer therapy within that timeframe.

All subjects will have hematology, serum chemistry, and urinalysis safety panels done at screening. Once dosing commences (Day 1), all subjects will be evaluated for safety, including serum chemistry, and hematology, once weekly for the first 4 weeks, every 2 weeks in Cycle 2 and monthly thereafter. PK/PD testing will be done in Cycle 1 and Cycle 2. The end of trial is defined as the point when the last subject on the study exits the study for any reason.

3.2 Sample Size

The trial seeks to exclude an uninteresting ORR of ≤15% (i.e., the response rate that might be associated with single-agent dexamethasone therapy [Anderson 2013]) in favor a target response rate of ≥40%. Considering a sample size of 19 subjects per cohort, the power to detect the difference between a null hypothesis response rate of 15% and an alternative-hypothesis response rate of 40% with a 0.025 one-sided significance level is 69% using a one-group, exact binomial test. A sample size of 19 subjects per cohort

will also provide a 97.5% 1-sided confidence interval centered around an expected ORR of 40% that excludes an ORR of 18.6% as a lower bound.

4. STUDY ENDPOINTS

4.1 Safety Endpoints

The safety of acalabrutinib with and without dexamethasone will be characterized by the type, frequency, severity, and relationship to study drug(s) of any treatment-emergent adverse events (AEs) or incidence of abnormalities of laboratory tests; serious adverse events (SAEs); or AEs leading to dose modification/delay or discontinuation of study treatment.

4.2 Efficacy Endpoints

Assessments of acalabrutinib efficacy in this study will be based on the criteria of standardized tumor response and disease progression for MM ([Rajkumar 2011] and [Blade 1998]).

- Overall response rate (ORR)
- Duration of response (DOR)
- Clinical benefit rate (CBR)
- Disease control rate (DCR)
- Progression-free survival (PFS)

4.3 Pharmacokinetic and Pharmacodynamic Parameters

Refer to separate reports for PK and PD parameters.

5. HYPOTHESES AND MULTIPLICITY

No formal statistical hypotheses will be tested. The clinical hypotheses are that acalabrutinib monotherapy and acalabrutinib + dexamethasone is safety and effective in subjects with R/R MM.

6. ANALYSIS SETS

6.1 All-Treated Population

All-treated population is defined as all enrolled subjects who receive ≥ 1 dose of any study drug. All-treated population will be used for evaluating the safety and efficacy unless otherwise specified.

6.2 Treatment Cohorts

Subjects are randomized with the ratio of 1:1 into 2 treatment cohorts to receive acalabrutinib, with or without dexamethasone:

- Cohort 1 (acalabrutinib monotherapy): acalabrutinib 100 mg bid continuously
- Cohort 2 (acalabrutinib + dexamethasone): acalabrutinib 100 mg bid continuously and 40 mg dexamethasone once weekly

7. INTERIM ANALYSIS AND EARLY STOPPING GUIDELINES

No formal interim analysis will be conducted.

8. FINAL ANALYSIS AND CLINICAL STUDY REPORT

The final analysis of primary and secondary efficacy endpoints will occur when last patient enrolled completes the end of Cycle 12, or withdraws for any reason and completes the 30-day follow-up visit, whichever occurs first. The CSR will be written based on the final analysis. The addendum of CSR will be written at the end of trial.

9. MISSING VALUES

9.1 Missing Safety Data

Conservative imputation rules will be applied partial dates 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. The algorithm for the imputation in Appendices 14.2 will be used. If dates are completely missing, no imputation will be made. Missing safety data other than partial or missing dates will not be imputed.

9.2 Missing Efficacy Data

The method of handing missing data and censoring data is described in the definition for the efficacy endpoints, mentioned at section 14.3.

10. STATISTICAL METHODS OF ANALYSIS

10.1 General Principles

Descriptive statistics will be used to summarize disposition, demographics, baseline characteristics, disease characteristics, prior anticancer therapy, concomitant medication, study drug administration, efficacy and safety outcomes. Descriptive summary of discrete data will be present the sample size and incidence as frequency and percentage. Descriptive summaries of continuous data will be present the sample size, group mean, standard deviation, median, and range.

Confidence intervals (CIs), when presented, will generally be constructed at the 95% level. For binomial variables, the exact method for CIs will be employed unless otherwise specified.

Calculation of time to event or duration of event (e.g., DOR) will be based on actual study day of event rather than nominal visit date.

10.2 Subject Disposition

Subjects are enrolled from 11 study sites of 2 countries. The number of subjects enrolled by region, country, and site will be presented. Subject disposition will be summarized for all enrolled subjects including the following information:

- Subject status on acalabrutinib
- Primary reasons for acalabrutinib discontinuation
- Subject status on the study
- Primary reasons for study discontinuation
- Time on the study

10.3 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.

10.4 Baseline Data

Summaries of demographics and baseline characteristics will be presented for subjects in the All-treated population. For continuous variables, n, mean, standard deviation,

median, minimum, and maximum values will be provided. For categorical variables, the number and percentage of subjects in each category will be summarized.

10.4.1 Demographics

- Sex (Male, Female)
- Age (year, continuous)
- Age category (<65 versus ≥65 years)
- Ethnicity
    - Hispanic or Latino
    - Not Hispanic or Latino
    - Not Reported
- Race
    - American Indian or Alaska Native
    - Asian
    - Black or African American
    - Native Hawaiian or Other Pacific Islander
    - White
    - Other
    - Not Reported
- Country
    - Unites States
    - United Kingdom

10.4.2 Baseline Characteristics

- Eastern Cooperative Oncology Group (ECOG) performance score
    - 0 = fully active.
    - 1 = restricted in physically strenuous activity
    - 2 = incapable of any work activity
    - 3 = limited self-care
    - 4 = completely disabled
- Height (cm)
- Weight (kg)

10.4.3 Baseline Disease Characteristics

- Time from initial diagnosis to first dose of acalabrutinib (months)

- Prior anticancer therapy regimens
    - Number of regimens (mean, standard deviation, median, minimum, maximum)
    - Number of subjects with regimens (1-3 regimens, >=4 regimens)
- Prior stem cell transplant
- MM stage by International Staging System (ISS) (stage I, II, III [Greipp 2005])
- MM subtypes
    - heavy chain subtypes
    - light chain subtypes
- Serum β2-microglobulin (<2.5, >=2.5 mg/L)
- Serum creatinine (<2, ≥ 2 mg/dL)
- Serum Hemoglobin (mean, standard deviation, median, min, max)
- Serum calcium (≤12, >12 g/dL)
- IgG (mean, median, min, max)
- IgA (mean, median, min, max)
- Bone marrow cellularity
    - Hypercellular
    - Normocellular
    - Hypocellular

10.5 Treatment and Medications

10.5.1 Prior Anticancer Therapies

A prior anticancer therapy is defined as a systemic therapy subjects received, either as a single or combination therapy, for the treatment of MM with an end date occurring before the date of first dose of study treatment. Therapies given as a consolidation or for maintenance of a response or remission will not be considered as a separate regimen. The prior anticancer therapy regimens will be summarized.

10.5.2 Prior and Concomitant Medications Received for Indications Other Than MM

Concomitant therapy is defined as all medications used on or after the first dose of study drug, through the treatment phase, and through 30 days following the last dose of study drug. Data reported on concomitant medications CRF pages will be used. Medications

started prior to first dose of study drug will be consider as prior treatment. Using this definition, a medication can be classified as both prior and concomitant. The start date and end date will be based on the rules provided in Appendices 14.2.1. Medications with completely missing start and stop dates will be considered as both prior and concomitant medications. Prior and concomitant medications other than antineoplastic agents or other systemic therapies for MM after enrollment will be coded by the World Health Organization (WHO) Drug Dictionary and summarized by Anatomic Therapeutic Chemical Classification System (ATC) level 2 (therapeutic subgroup) and level 5 (preferred term/chemical ingredient).

10.5.3 Exposure to Study Drugs

Separate analysis will be performed for acalabrutinib and dexamethasone. Descriptive statistics (n, mean, standard deviation, median, minimum and maximum values) will be used to summarize:

- Duration of exposure (the interval between first dose date and last dose date)
- Actual cumulative dose administered
- Average dose (the ratio of actual cumulative dose administered and Duration of exposure): daily dose for acalabrutinib and weekly dose for dexamethasone
- Relative dose intensities (the percentage of actual cumulative dose to the planned cumulative dose)

The reasons for acalabrutinib dose withholding and reduction will be summarized and presented as the number and percentage of subjects with non-missing data per category.

- Dose withholding of acalabrutinib is defined as missing dose for ≥ 7 consecutive days.
- Dose reduction defined as taking lower dose level (100 mg per day) for acalabrutinib for ≥ 3 consecutive days.

10.6 Analyses of Safety Endpoints

Safety analyses will be performed on All-treated population by treatment cohort.

Analyses of adverse events (AEs) will be performed on treatment-emergent AE (TEAE) data, unless otherwise specified. TEAEs are defined as those events with onset or

worsen date on or after the date of first dose of acalabrutinib, through the treatment phase to last dose of acalabrutinib, and within 30 days following the last dose of acalabrutinib, whichever is later. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 or higher is used for AE grading.

Treatment-emergent AEs will be summarized in 3 groups: (1) acalabrutinib monotherapy, (2) acalabrutinib + dexamethasone, and (3) crossover from monotherapy to acalabrutinib + dexamethasone therapy. By this grouping method, AEs among subjects assigned to acalabrutinib monotherapy will be reported in group 1 when AEs occurred before crossover, and AEs occurred on/after crossover will be reported in group 3. Treatment-emergent AEs occurred on or after crossover will be summarized in the crossover group. Treatment-emergent AEs occurred before crossover will be summarized in the monotherapy group. All AE terms will be coded by Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1 and will be presented by system organ class (SOC) and preferred term (PT). Treatment-emergent AEs will be summarized by SOC and PT and by CTCAE toxicity grade. The drug-related AEs, serious adverse events (SAEs) and drug-related SAEs, AEs leading to treatment discontinuation, dose delay and dose modification will be summarized by PT by CTCAE toxicity grade.

Death will be reported in a listing and summarized. A table will be provided for grade 5 AE and the relationship with any study drug.

10.6.1 Adverse Events of Clinical Interest

In addition to general analyses of adverse events, analyses will be conducted on selected AEs of clinical interest. The following are event of clinical interests (ECIs): cardiac events (including atrial fibrillation), anemia, cytopenias, hemorrhage including major hemorrhage, hepatic events, hypertension, infections, interstitial lung disease and pneumonitis, second primary malignancies, and tumor lysis syndrome. Details of ECIs is summarized in the Appendices of this SAP.

AEs of clinical interest are defined in section 14.4 of the appendices.

Subject incidence rates of AEs of clinical interest will be tabulated by treatment cohorts and all-treated population.

10.6.2 Laboratory Abnormality

All of the laboratory tests are performed in central laboratory and/or in local laboratory. Analyses will be performed for laboratory test data collected at baseline and from first exposure to acalabrutinib to 30 days after last dose of acalabrutinib or up to the safety follow-up visit date, whichever is later. Laboratory test for hematology, serum chemistry, and T/B/NK cell count up will be performed in central laboratory with reference range and the results will be reported in standard international units or conventional units when appropriate. Applicable laboratory test results will be graded according to CTCAE Version 4.03 or higher. AMA (American Medical Association (AMA) Manual of Style 10th Edition 2017) laboratory values will be applied whenever reference ranges are not available (e.g., local laboratory data).

For selected laboratory test parameters, summary statistics (mean, standard deviation, median, minimum and maximum) will be produced at baseline, post-baseline values from the last visit, minimum and maximum post-baseline values, and changes of these post-baseline values from baseline. Post-baseline toxicity grade greater than baseline grade will be presented in the treatment-emergent laboratory abnormality table. Shift from baseline to the worst grade from first exposure to acalabrutinib to 30 days after last dose of acalabrutinib or up to the safety follow-up visit date, whichever is later, will be provided as shift tables for selected parameters.

To be included in the summary table, a subject must have at least one post-baseline value for the given time point.

- *Lymphocytosis*

Lymphocytosis is defined as an elevation in absolute lymphocyte count (ALC) of ≥ 50% compared to baseline and a post-baseline assessment >5x10^9/L (Wang 2013). 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) a decrease of ALC value that is below 5x10^9/L, whichever occurs first. 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.

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.

Summary statistics will be provided for time to lymphocytosis. KM estimates for DOL will be provided.

- *Hepatitis B Test*

Subjects with a history of hepatitis B virus (HBV) infection should be monitored monthly with a quantitative polymerase chain reaction (PCR) test for HBV DNA. Monthly monitoring should last until 12 months after last dose of acalabrutinib. Any subject with a rising viral load (above lower limit of detection) should discontinue study drug and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B. A listing of subjects with any hepatitis B test will be provided.

10.6.3 **Vital Signs**

Analyses will be performed for vital sign safety data collected at baseline and from first exposure to acalabrutinib to 30 days after last dose of acalabrutinib or up to the safety follow-up visit date, whichever is later. Summary statistics (mean, standard deviation, median, minimum and maximum) will be produced for vital signs at baseline, post-baseline values from the last visit, minimum and maximum post-baseline values, and changes of these post-baseline values from baseline. In addition, blood pressure is graded and the maximum post-baseline grade will be presented. Systolic Blood Pressure is graded by CTCAE as Grade 0 (<= 119 mm Hg), Grade 1 (120-139 mm Hg), Grade 2 (140 – 159 mm Hg), Grade 3 (>= 160 mm Hg). Diastolic Blood Pressure is grade as Grade 0 (<= 79 mm Hg), Grade 1 (80 -89 mm Hg), Grade 2 (90 – 99 mm Hg), Grade 3 (>= 100 mm Hg). In order to be included in the table, a subject must have at least one post-baseline value for the given time point.

10.6.4 **ECOG Performance Score**

Change of ECOG score from baseline to the worst score during the period from first exposure to acalabrutinib to 30 days after last dose of acalabrutinib or up to the safety follow-up visit date, whichever is later will be provided as shift tables.

10.6.5 Electrocardiogram

ECG data are collected at screening. The investigator assessment of clinical significance categorized as normal, abnormal but not clinically significant, and abnormal clinically significant will be summarized. The number of subjects with corrected QT interval (QTc) greater than 480 msec will also be provided. A listing of subjects with abnormal and clinically significant baseline ECG results or QTc> 480 msec will be provided.

10.7 Analyses of Efficacy Endpoints

10.7.1 Definitions

Study treatment response will be assessed according to response criteria of standardized tumor response and disease progression for MM ([Rajkumar 2011] and [Blade 1998]) including stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), minimal response (MR), stable disease (SD), and disease progression. Overall response data will be summarized as follows:

- Overall Response Rate

ORR is defined as the proportion of subjects who achieve a sCR, CR, VGPR, or PR.

- Clinical Benefit Rate

Clinical benefit rate (CBR) is defined as the proportion of subjects who achieve a sCR, CR, VGPR, PR, or MR.

- Disease Control Rate

Disease control rate (DCR) is defined as the proportion of subjects who achieve a sCR, CR, VGPR, PR, MR, or SD.

- Duration of Response (DOR)

DOR is defined as the interval from the first documentation of sCR, CR, VGPR or PR to 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 definitive MM progression was objectively documented. Data from subjects who have

MM progression or die after ≥ 2 consecutive missing tumor assessments will be censored at the last time before the missing assessments that lack of MM progression was objectively documented. The censoring rules for analyses of DOR are summarized in Appendix 14.3.

- Progression-free Survival (PFS)

PFS is defined as the interval between the date of randomization to any study cohort and the first documentation of objective MM 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 MM progression was objectively documented. Subjects who have MM progression or die after ≥ 2 consecutive missing tumor assessments will be censored at the last time that lack of MM progression was objectively documented before the missing assessments. The censoring rules for analyses of PFS are summarized in Appendix 14.3.

10.7.2 Analysis Methods

The analysis of ORR, CBR, DCR, and PFS will be conducted on the All-treated Population. The analysis of DOR will be conducted on the subset of the All-treated Population who achieve sCR, CR, VGPR or PR as their best overall response.

ORR, CBR, DCR will be calculated and the corresponding 95% two-sided confidence intervals will be derived. DOR and PFS will be estimated using the Kaplan-Meier (KM) method. KM estimates with 95% CIs will be calculated for event time quartiles, including median. In addition, listings for DOR and PFS will be provided, including the reason for censoring.

11. DISEASE BIOMARKERS

The relationship between biological markers in MM cells and response to therapy will not be explored, due to the fact that a very small number of subjects has responded to study treatment.

12. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

There is no major change from protocol-specified analyses.

Due to the fact that a very small number of subjects has responded to study treatment, there will not be an exploration of drug response and biological markers.

13. LITERATURE CITATIONS / REFERENCES

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14. APPENDICES

14.1 Definitions

14.1.1 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 acalabrutinib. 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.

14.2 Imputation Rules

14.2.1 Partial or Missing Dates

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, the first dose date will be used, or if the imputed AE start date is after the AE end date, 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, 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.

If death year and month are available but day is missing:

- If mmyyyy for last contact date = mmyyyy for death date, set death date to the day after the last contact date.
- If mmyyyy for last contact date < mmyyyy for death date, set death date to the first day of the death month.
- If mmyyyy for last contact date > mmyyyy for death date, data error and do not impute.

If both month and day are missing for death date or a death date is totally missing, no imputation is made.

14.3 Censoring Rules for Duration of Response and Progression-Free Survival

Situation	Outcome	Event Description or Censoring Reason	Last Analysis Date
Documented disease progression before initiation of new anticancer therapy or on/before data cutoff date, whichever occurred first, also no more than 1 missing tumor assessments before documented disease progression	Event	Progressive Disease	Earliest date of documented disease progression
Death before initiation of new anticancer therapy or on/before data cutoff date, whichever occurred first	Event	Death	Date of Death
New anticancer therapy Initiated before data cutoff date and before documented disease progression or death	Censored	New anti-cancer therapy	Date of last adequate tumor assessment prior to initiation of new anticancer therapy
New anti-cancer therapy before data cutoff date for subjects without documented disease progression or death	Censored	New anti-cancer therapy	Date of last adequate tumor assessment prior to initiation of new anticancer therapy
No documented disease progression, initiation of new anticancer therapy or death on/before data cutoff date	Censored	Data cutoff	Date of last adequate tumor assessment on or before data cutoff date
No post-baseline adequate disease assessments	Censored	No post-baseline adequate disease assessments	Date of first dose of study drug

14.4 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 BTK inhibitor. The AEs selected for dedicated analysis were evaluated using Standardized MedDRA Queries (SMQs), where available, by SOC, or by sponsor defined baskets of MedDRA Adverse Event Grouped Terms.

Category name	**Sub-category name**	**Definition for SAP**	**Additional Criteria for Narratives**
Cardiac events		SOC Cardiac disorders	No additional criteria
	Atrial fibrillation	PT Atrial fibrillation PT Atrial flutter	Any
Cytopenias-Anemia		SMQ Haematopoietic erytheropenia [narrow + broad]	No additional criteria
Cytopenias-Leukopenia		SMQ Haematopoietic leukopenia [narrow + broad]	No additional criteria
	Neutropenia	• PT Febrile neutropenia • PT Neutropenia • PT Neutropenic infection • PT Neutropenic sepsis • PT Neutrophil count decreased • PT Neutrophil percentage	No additional criteria
	Other Leukopenia	SMQ Haematopoietic leukopenia [narrow + broad] excluding PTs for neutropenia above	No additional criteria
Cytopenias - Thrombocytopenia		SMQ Haemorrhage terms (excluding laboratory terms)	No additional criteria
	Major Hemorrhage	As per Acerta definition (Appendences)	Any
Hepatic Events		• SMQ [narrow] Hepatic failure, fibrosis and cirrhosis and other liver damage related conditions • SMQ [narrow] Liver related investigation signs • SMQ [narrow] Hepatitis, non-infectious	PTs of Grade ≥3 as below • Alanine aminotransferase abnormal • Alanine aminotransferase increased • Aspartate aminotransferase abnormal • Aspartate aminotransferase increased • Hepatic enzyme abnormal • Hepatic enzyme increased • Hypertransminasemia

			• Liver function test abnormal • Liver function test increase • Transaminases abnormal • Transaminases increased Subjects who fulfill biochemical Hy's law criteria defined as below: ≥ 3 x ULN AST or ≥ 3 x ULN ALT and ≥ 2 x ULN total bilirubin At the same visit
Hypertension		• SMQ Hypertension [narrow]	No additional criteria
Infections		• SOC Infections and infestations	No additional criteria
Interstitial lung disease/Pneumonitis		• SMQ [narrow] Interstitial lung disease	No additional criteria
Second primary malignancies		• SMQ Malignant or unspecified tumors and SMQ Myelodysplastic syndrome (narrow), excluding skin (i.e. exclude SMQ Skin neoplasms, malignant and unspecified)	Any
Tumor lysis syndrome		• PT Tumor lysis syndrome	Any

MedDRA version 19.1

- No additional criteria means only SAE, AE leading 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.