ACE-CL-006: Statistical Analysis Plan

A Randomized, Multicenter, Open-Label, Non-Inferiority, Phase 3 Study of ACP-196 Versus Ibrutinib in Previously Treated Subjects with High Risk Chronic Lymphocytic Leukemia

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Date

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Date

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SAP Revision History:

Version / Date	Summary of Major Changes and Rationale
Final, July 8, 2015	
Amendment 1.0, October 23, 2020	1. Specified that blinded aggregate data summaries will be created using dummy treatment codes prior to study database lock, for clarification on the method - Section 1, Section 2.7.2 2. Refreshed study design and objectives with most recent text from protocol for consistency across study documents, including a clarifying update to CCI [redacted] made in Protocol Amendment 5 – Section 2 3. Specified data cutoff date for final analysis, as it has been finalized – Section 2.5 4. Updated multiplicity testing procedure based on available data from ibrutinib and acalabrutinib studies as well as FDA NI Guideline (moved atrial fibrillation from second to first in the hierarchical testing order for secondary endpoints) – Section 2.6 5. Removed the testing of superiority on the primary endpoint, PFS, that was not part of the gate-keeping procedure – Section 2.9. 6. CCI [redacted] 7. Added handling instructions for subjects in the safety population who incorrectly received both study treatments – Section 3.2, Section 7.2.1, Section 8 8. Updated per protocol population definition to reference most recent version of protocol eligibility criteria for consistency, specified amount of incorrect treatment that will result in a subject being excluded – Section 3.3 9. Removed section on visit window calculation, as the planned analyses do not require it – Section 4 10. Added steps for determining whether assessments on day of first dose are considered baseline; specified baseline definition for subjects not treated, to clarify how these cases will be handled – Section 4.1.1 11. Added definitions for prior and subsequent anticancer therapy and updated definition for concomitant therapies to consider

	start date of subsequent anticancer therapy – Section 4.1.3, Section 4.1.4 12. Added imputation rules for date last known alive to address the possibility of partial dates in the data – Section 4.2.3 13. Added imputation rules for laboratory values below or above the level of quantification to address this possible case in the data – Section 4.2.4 14. Added new categories of interest to list of baseline disease characteristics – Section 5.3.2 15. Added summary of medical history as it is standard for the CLL studies – Section 5.4 16. Moved definitions for duration of exposure, average daily dose, and relative dose intensity from Section 4.1, Definitions, to Section 6.3, Study Treatment Exposure, for more logical location in the document – Section 6.3 17. Added tabulations of study treatment withholding and reduction based on the dosing log to align with other acalabrutinib CLL studies – Section 6.4 18. Moved the pooling strategy for the stratified analyses from Section 4, General Conventions, to Section 7, Efficacy Analysis, for more logical location; changed the collapsing threshold to <2 events in a stratum (instead of <30 subjects), and allowed for collapsing of >1 stratum to plan for the possibility of sparse data and align with the method used for other acalabrutinib CLL studies – Section 7 19. Specified censoring rules for PFS, updated sensitivity and subgroup analyses for primary endpoint based on FDA review comment for CLL pivotal studies – Section 7.1 20. Clarified that analysis of secondary endpoints related to safety will be based on the safety population; removed use of chi-squared test for secondary endpoints since Cochran-Mantel-Haenszel is the planned test in the protocol; added subgroup analyses – Section 7.2.1 21. Specified censoring rules for OS for clarity, added subgroup analysis for OS – Section 7.2.2 22. Moved CCI [redacted] to exploratory analysis per Protocol Amendment 5 – Section 7.3.1 23. CCI [redacted] 24. CCI [redacted]

	25. CCI [redacted] 26. CCI [redacted] 27. CCI [redacted] 28. Revised adverse events of special interest/other adverse events of interest into adverse events of clinical interest to align with the CLL pivotal studies, and adverse events of special interest which includes only ventricular arrythmia in accordance with Protocol Amendment 5 – Section 8.1.3, Appendix 1 29. Added subgroup analyses for adverse events to further explore the risk:benefit of acalabrutinib versus ibrutinib – Section 8.1.4 30. Added analysis of serum immunoglobulins as they are part of the schedule of assessments – Section 8.3.4 31. Add summary of electrocardiogram abnormalities, as a post-baseline ECG is performed at the early termination/safety follow-up visit – Section 8.6 32. CCI [redacted] 33. Added search strategy for narratives – Appendix 2

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LIST OF ABBREVIATIONS AND DEFINITIONS

11q del	11q deletion mutation, chromosome deletion 11q22.3
17p del	17p deletion mutation, chromosome deletion 17p13.1
AE	adverse event
AESI	adverse event of special interest
ALC	absolute lymphocyte count
ATC	Anatomical Therapeutic Chemical
BID	twice per day
BTK	Bruton's tyrosine kinase
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CLL	chronic lymphocytic leukemia
CCI [redacted]	
CCI [redacted]	
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
CCI [redacted]	
CCI [redacted]	
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
CCI [redacted]	

CCI [redacted]	
CCI [redacted]	
FDA	U.S. Food and Drug Administration
HR	hazard ratio
IGHV	immunoglobulin heavy-chain variable
IRC	independent review committee
IPD	important protocol deviation
ITT	intent-to-treat
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
IWRS	Interactive Web Response System
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
CCI [redacted]	
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NI	non-inferiority
CCI [redacted]	
CCI [redacted]	
OS	overall survival
PD	progressive disease
PFS	progression free survival
PK	pharmacokinetic
PP	per protocol

CCI [redacted]

CCI [redacted]

CCI [redacted]

QD	once per day
RBC	red blood cell
SAP	statistical analysis plan
SD	stable disease
SMQ	standardized MedDRA query
SOC	system organ class
TEAE	treatment emergent adverse event

CCI [redacted]

WHO	World Health Organization

1 INTRODUCTION

This statistical analysis plan (SAP) provides details of the statistical analyses that have been outlined for study ACE-CL-006 Protocol Amendment 5, dated October 21, 2020, which is titled “A Randomized, Multicenter, Open-Label, Non-Inferiority, Phase 3 Study of ACP-196 Versus Ibrutinib in Previously Treated Subjects with High Risk Chronic Lymphocytic Leukemia .”

This study is being conducted under the sponsorship of Acerta Pharma BV. The Sponsor is conducting statistical programming and analyses using dummy treatment code before study database lock to minimize bias on study conduct and analyses. All safety and efficacy analyses for the purpose of independent Data Monitoring Committee (DMC) review will be conducted in an unblinded fashion with results summarized by treatment arm under contract with an independent Statistical Data Analysis Center.

2 STUDY DESCRIPTION

2.1 Study Design

This randomized, multicenter (ie, approximately 200 global centers), open-label, non-inferiority Phase 3 study is designed to evaluate the efficacy and safety of acalabrutinib (ACP-196) versus ibrutinib in subjects with relapsed or refractory chronic lymphocytic leukemia (CLL) who have high-risk prognostic markers (eg, 17p del and/or 11q del) per National Comprehensive Cancer Network (NCCN) guidelines (NCCN Version 1. 2016).

Approximately 500 eligible subjects will be randomized in a 1:1 ratio into 2 arms to receive either acalabrutinib 100 mg BID (Arm A; N=250) or ibrutinib 420 mg QD (Arm B; N=250).

This study will use an Interactive Web Response System (IWRS) for randomization. Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced, and to enhance the validity of statistical comparisons across treatment groups.

Randomization will be performed stratified by the following factors:

- Presence of 17p del
- Eastern Cooperative Oncology Group (ECOG) performance status (ECOG = 2 versus ECOG ≤1)

- Number of prior therapies (1-3 versus ≥ 4)

An independent DMC will be formed and constituted according to regulatory agency guidelines. Detailed information regarding the composition of the DMC and detailed DMC procedures will be provided in a separate charter. The DMC will review the safety data periodically and provide recommendations according to the charter.

2.2 Study Objectives

2.2.1 Primary Objective

To assess whether acalabrutinib is non-inferior to ibrutinib with respect to progression free survival (PFS), based on Independent Review Committee (IRC) assessment, in subjects with relapsed or refractory CLL with high-risk prognostic markers.

2.2.2 Secondary Objectives

2.2.2.1 Efficacy Objectives

To evaluate the benefit:risk of acalabrutinib versus ibrutinib in terms of:

- Grade ≥ 3 infections
- Richter's transformation
- Atrial fibrillation
- Overall survival (OS)

2.2.2.2 Safety Objective

The safety and tolerability including adverse events (AEs) of interest and laboratory assessments

2.2.3 Exploratory Objectives

CCI

2.3 Non-Inferiority (NI) Margin and Sample Size Justification

The NI margin of CCI, with regard to median PFS, was selected to ensure that the efficacy of acalabrutinib will not be substantially inferior to ibrutinib in the event of a positive statistical outcome for the study. Assuming the median PFS for the ibrutinib arm is CCI, and the time-to-event is exponentially distributed, a CCI in median PFS would be CCI for acalabrutinib.

The CCI for median PFS translates into a hazard ratio (HR) scale margin of 1.429, which was selected using the fixed margin method described in the U.S. Food and Drug Administration (FDA) Guidance for Industry: Non-Inferiority Clinical Trials (2010). This method, which is also in line with Committee for Medicinal Products for Human Use (CHMP) Guidance on the Choice of the Non-inferiority Margin (2005), uses a 2-step procedure to select the NI margin:

1. Determine M_1 (as per FDA terminology), the entire effect of the active control (ibrutinib) assumed to be present in the NI study from historical data;
2. Determine M_2 (as per FDA terminology), the largest clinically acceptable difference (degree of inferiority) of the test drug (acalabrutinib) compared to the active control (ibrutinib).

As the FDA Guidance describes, M_2, the pre-specified NI margin the non-inferiority study should meet, must never be greater than M_1.

Ofatumumab is currently used for the treatment of patients with CLL (NCCN Version 2.2015). In the RESONATE study (Byrd 2014a), ibrutinib demonstrated superiority over ofatumumab in PFS in an all-comers setting as well as in patients in the high-risk 17p del and 11q del populations. The primary results of the study are summarized in Table 1 and provide the basis for choosing the NI margin.

Table 1. Ibrutinib Data from RESONATE Study (Byrd 2014a)

	Sample size	CCI
All patients	391	
17p del	127	
11q del	122	

M_1, calculated as CCI [redacted] is estimated to be CCI [redacted] The CCI [redacted] is used to account for the lack of information on study-to-study variability from a single historical study. The CCI [redacted] translates into the CCI [redacted]

Based on the median PFS for subjects with 17p del or 11q del treated with ibrutinib in the Phase 2 study (Byrd 2014b), we assume the median PFS of ibrutinib (based on IRC assessment) in this study will be approximately CCI [redacted] As described above the CCI [redacted] on median PFS translates into a HR of 1.429 (M_2) for acalabrutinib versus ibrutinib. The selected M_2 of 1.429 CCI [redacted]

Assuming CCI [redacted] for PFS and an NI margin of 1.429, a sample size of 500 subjects (randomized 1:1 to each of the 2 arms) will provide 80% power at a 1-sided, 0.025 significance level to test the non-inferiority hypothesis. The accrual period is assumed to be about CCI [redacted] with a follow-up period of approximately CCI [redacted] after the last subject enters the study. The calculation assumes over the course of the study, CCI [redacted] The NI test will be performed when approximately 250 PFS events have been observed. Based on these assumptions, the CCI [redacted]

The sample size and power calculations were based on East 6 (Version 6.3.1), with use of the design "Two-Sample Test, Parallel Design, Logrank Given Accrual Duration and Study Duration."

2.4 Interim Analysis

No interim analysis for efficacy is planned for this trial.

An independent DMC will monitor safety during the study on a regular basis. The committee will operate independently of the Sponsor and the clinical investigators. A DMC charter will describe the details regarding DMC membership, schedule and format of meetings, format for presentation of data, access to data, method and timing of providing safety reports to the DMC, and other issues relevant to committee operations.

The DMC members will use their expertise, experience, and judgment to evaluate the safety data from the trial and to recommend to the Sponsor whether the trial should

continue or be stopped early for safety. No formal statistical rules recommending early stopping for safety are planned.

2.5 Final Analysis

The sponsor has monitored total number PFS events across treatment arms closely, where primary analysis for progression is based on IRC assessment. A CCI [redacted] has been determined based on projection of the timing of planned 250 events have been reported in the database. Database lock will occur after all data through the data cutoff date have been entered and cleaned. The final analysis will be conducted based on final locked database which consists of all available data, including all available PFS events, up to the data cutoff date.

2.6 Multiplicity Adjustments

The primary endpoint of the study is PFS. The hypothesis to be evaluated in the analysis of the primary efficacy endpoint is that acalabrutinib is not inferior to ibrutinib where non-inferiority is defined by a pre-specified margin. If the upper bound of the 2-sided 95% CI for the HR is below 1.429, ACP-196 will be concluded to be non-inferior to ibrutinib.

The gate-keeping strategy will be implemented to control the family-wise error rate at the 0.05 level when performing multiple testing on primary and secondary endpoints. Specifically, if acalabrutinib is shown to be non-inferior to ibrutinib, the superiority of each of the secondary endpoints listed below will continue to be tested at a 2-sided 0.05 significance level in a pre-specified order until the statistical significance is not reached:

1. Incidence of atrial fibrillation
2. Incidence of grade ≥ 3 infections
3. Incidence of Richter's transformation
4. OS

Following the fixed sequence testing procedure, if a p-value is not statistically significant, the p-value for subsequent tests will be presented as descriptive.

The hierarchical order is determined according to estimated statistical power based on information from currently available data from ibrutinib studies and acalabrutinib studies.

2.7 Randomization and Blinding

2.7.1 Randomization

Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (e.g., demographic and baseline characteristics) are evenly balanced, and to enhance the validity of statistical comparisons across treatment groups.

Central randomization will be implemented through use of IWRS. Subjects will be randomized in a 1:1 ratio to receive either acalabrutinib or ibrutinib with the following stratification factors:

- Presence of 17p del (yes, no)
- ECOG performance status (ECOG = 2 versus ECOG ≤1)
- Number of prior therapies (1-3 versus ≥ 4)

The randomization code will be controlled through a centralized procedure and will not be known to study and site personnel or the subject before the subject is randomized into the study.

2.7.2 Blinding

In this open-label study, neither the subjects nor the investigators will be blinded to treatment. However, access to treatment randomization by IWRS will be controlled so that the sponsor's staff overseeing the conduct of the study or analyzing/summarizing data will not have aggregated efficacy or safety summary by randomized treatment arm before Sponsor unblinding for final analysis. Dummy treatment codes will be used to set up statistical programming prior to Sponsor unblinding for final analysis.

Response assessment will be performed centrally by the IRC. An Independent Review Charter for IRC will be created to describe details of data review, data flow, and work flow.

3 ANALYSIS POPULATIONS

3.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) population is defined as all subjects randomized. All efficacy analyses will be performed using the ITT population and will be analyzed as randomized, following “intent-to-treat” principle, unless specified otherwise. In addition, the ITT

population will be used to summarize demographics, as well as baseline and disease characteristics.

3.2 Safety Population

The safety population includes all subjects who received at least one dose of study drug. The safety population will be the analysis population for safety analyses. Subjects will be analyzed as treated. If a subject incorrectly received both acalabrutinib and ibrutinib in any amount, the subject will be analyzed under the acalabrutinib arm, as a conservative approach.

3.3 Per Protocol Population

The per protocol (PP) population includes subjects in the ITT population with exclusion of:

- Subjects with < 75% relative dose intensity.
- Violated protocol inclusion or exclusion criteria that may affect interpretation of efficacy (Inclusion Criteria #3, #5, #6, Exclusion Criteria #2-4 and #6-9 in Protocol Amendment 5 dated 21 Oct 2020, and Inclusion Criterion #7 from Protocol Amendment 4 dated 14 Dec 2017).
- Received the incorrect treatment for ≥7 days.

3.4 CCI [redacted]

CCI [redacted]

4 GENERAL CONVENTIONS

Continuous data will be summarized using descriptive statistics (number of observations, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum). Frequencies and percentages will be used for summarizing categorical (discrete) data.

Confidence intervals, when presented, will generally be constructed at the 2-sided 95% level. For binomial variables, the normal approximation methods will be employed unless otherwise specified.

Calculation of time to event or duration of event endpoints will be based on the study day of the event or censoring date rather than visit number or visit label. Missing efficacy or safety data will not be imputed unless otherwise specified.

The following rules will be used for the days to months/years conversion:

- 1 month=30.4375 days
- 1 year=365.25 days.

All summaries will be presented by treatment arm unless otherwise specified. Data will be presented in data listings by treatment arm and subject number.

4.1 Definitions

4.1.1 Definition of Baseline and Post-Baseline Value

For safety parameters, baseline is defined as the last measurement taken prior to the first dose of study drug. A post-baseline value is defined as a measurement taken after the first dose of study drug.

For efficacy parameters, the baseline value is defined as the last measurement taken prior to or on the date of randomization; a post-baseline value is defined as a measurement taken after the date of randomization.

The baseline and post-baseline definitions for laboratory parameters are similarly defined as those for safety parameters. For laboratory parameters used for response assessment, baseline values will be defined in reference to first dose date of study drug.

For assessments on the day of first dose where time is not captured, a nominal pre-dose indicator, if available, will serve as sufficient evidence that the assessment occurred prior to first dose. Assessments on the day of first dose where neither time nor a nominal pre-dose indicator are captured will be considered prior to first dose if such procedures are required by the protocol to be conducted before first dose.

For subjects who were not treated, the baseline is defined as the last valid assessment on or before date of randomization within the study.

4.1.2 Definition of Study Day

For efficacy data summary, the study day will be calculated in reference to the date of randomization. Study Day 1 for efficacy data is defined as the date of randomization. For visits (or events) that occur on or after randomization, study day is defined as (date of visit [event] – date of randomization + 1). For visits (or events) that occur prior to randomization, study day is defined as (date of visit [event] – date of randomization).

For safety data, study day will be calculated in reference to the first dose date of study drug. Study Day 1 for safety data analysis is defined as the first dose date of study drug. For visits (or events) that occur on or after first dose date, dose day is defined as (date of visit [event] – date of first dose of study drug + 1). For visits (or events) that occur prior to first dose date, dose day is defined as (date of visit [event] – date of first dose of study drug).

4.1.3 Definition of Prior and Concomitant Therapy

For the purpose of inclusion in prior and/or concomitant medication or therapy tables, incomplete medication or radiation start and stop dates will be imputed as detailed in Section 4.2. Based on imputed start and stop dates:

- Prior medications/procedures/radiation therapies are defined as medications with a start date occurring before the date of first dose of study drug.
- Concomitant medications/procedures/radiation therapies are defined as medications that:
    - Had start date between the first dose date of study drug, 30 days after the last dose of study drug, or the first dose date of new anticancer therapy for CLL, whichever is earlier, or
    - Had start date before first dose date and stopped or continued after first dose date.
- In addition, medications/procedures/radiation therapies that meet the criteria for both prior and concomitant medications will be classified as both prior and concomitant medication.

4.1.4 Prior and Subsequent Anticancer Therapy for CLL

For the purpose of inclusion in the prior and/or subsequent anticancer therapy tables, incomplete medication start dates will be imputed as detailed in Section 4.2. The start date of anticancer therapy is defined as the first dose date of the therapy. Based on imputed start dates:

- Prior anticancer therapies are defined as medications that had an indication for the primary malignancy CLL and had a start date occurring before the date of first dose of study drug.
- Subsequent anticancer therapies are defined as medications that had an indication for the primary malignancy CLL and had a start date after the date of last dose of study drug.

4.1.5 Time on Study

Time on study will be calculated from the date of randomization to the study exit date, as follows:

Time on study = study exit date - date of randomization + 1 day.

4.1.6 Treatment Emergent Period

The treatment emergent period is defined as the period of time from the date of the first dose of study drug through 30 days after the date of the last dose of study drug or the first date starting new anticancer therapy for CLL, whichever is earlier.

4.2 Imputation Rules for Missing and Partial Data

In general, other than for partial dates, missing data will not be imputed and will be treated as missing. The algorithms for imputation of partial dates vary depending upon the parameter.

4.2.1 Adverse Events, Concomitant Medications, Prior/Subsequent Anticancer Therapies, Initial Diagnosis

Imputation of partial dates will be made for AE onset and stop dates, start and end dates of concomitant medication, start date of prior/subsequent anticancer therapy, and date of initial diagnosis. 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 imputated date for initial diagnosis or prior anticancer therapy is on or after date of randomization, then date of randomization – 1 will be used. If such imputed date for

subsequent anticancer therapy is before date of last dose, then 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 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, then the death date will be used, or if the imputed AE end date is before the AE start date, then the AE start date will be used.

4.2.2 Death Dates

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, do not impute and censor the subject survival time.

4.2.3 Date Last Known Alive

If year and month of date last known alive are available but day is missing, set date to the 1st of the month.

If both month and day are missing, set date to January 1st of the year.

4.2.4 Laboratory Values

Laboratory values below the lower level of quantification (Q) that are reported as “<Q” or “≤Q” in the database will be imputed by Q x 0.99 for analysis purposes. However, the original value will be reported in the listings.

Laboratory values above the upper level of quantification (Q) that are reported as ">Q" or "≥Q" in the database will be imputed by Q x 1.01 for analysis purposes. However, the original value will be reported in the listings.

4.3 Software

Sample size calculation was performed using East 6 (Version 6.3.1). Statistical analyses and data summary will be conducted using SAS Version 9.4 or higher.

5 STUDY POPULATION SUMMARIES

5.1 Study Disposition

Enrollment for subjects randomized will be summarized by region, country, and study center. Subject disposition will be summarized categorically and will include the number and percentage of subjects in each analysis population. Subject disposition data including subject status on treatment, subject status on the study, time on study, and time from randomization to first dose will be summarized by treatment arm.

5.2 Protocol Deviations

Number and percentage of subjects with important protocol deviations (IPDs) after randomization will be summarized by treatment arm. A listing of subjects with IPDs will be produced. IPD categories, subcategory codes, and descriptions will be defined by sponsor IPD guidance and used during the course of the study. The sponsor will review IPDs throughout the study prior to database lock. The final IPD list will be used to produce the IPD summary table and listing.

5.3 Demographics and Baseline

5.3.1 Demographics and Baseline Characteristics

The following demographic and baseline characteristics will be summarized:

- Age at informed consent (continuous)
- Age category (< 65, ≥ 65; <70 vs. ≥70; < 75, ≥ 75)
- Sex (male, female)
- Race

- Ethnicity
- Height (cm)
- Weight (kg)
- Body surface area (m^2), calculated as $\sqrt{\text{height (cm) * weight (kg)/3600}}$
- ECOG performance status (2 vs ≤1)
- Region (North America, Western Europe, Central and Eastern Europe, Asia Pacific)

5.3.2 Baseline Disease Characteristics

The following baseline disease characteristics will be summarized:

- Time (months) from initial diagnosis to randomization
- Time (months) from prior treatment to randomization
- Bulky disease (<5 cm, ≥5 cm; <10 cm, ≥10 cm)
- Rai stage (0, I, II, III, and IV)
- Binet Stage (A, B, and C)
- 17p del and/or 11q del (yes, no)
- 17p del (yes, no)
- 11q del (yes, no)
- TP53 mutation (mutated, unmutated)
- Immunoglobulin heavy-chain variable (IGHV; mutated, unmutated)
- Complex karyotype (yes, no)
- β_2-microglobulin (mg/L) group at baseline (≤3.5 mg/L, >3.5 mg/L)
- High risk features:
    - 17p del and 11q del (yes, no)
    - 17p del and/or TP53 mutation (yes, no)
    - 17p del and TP53 mutation (yes, no)
    - 17p del and 11q del and TP53 mutation (yes, no)
    - 17p del and unmutated IGHV (yes, no)
    - 17p del and complex karyotype (yes, no)
    - 11q del and complex karyotype (yes, no)
- Cytopenia at baseline
    - Neutropenia - ANC ≤l.5 x 10^9/L (yes, no)
    - Anemia - Hgb ≤11 g/dL (yes, no)
    - Thrombocytopenia - platelet counts ≤100 x 10^9/L (yes, no)
    - Any of the above (yes, no)
    - All of the above (yes, no)

- Prior red blood cell (RBC) transfusion within 28 days before randomization
- Prior platelet transfusion within 28 days before randomization
- Constitutional symptoms (weight loss, fever, night sweats, fatigue)
- Creatinine clearance (mL/min)
- Absolute lymphocyte counts (10^9/L)
- Absolute neutrophil count (10^9/L)
- Platelet count (10^9/L)
- Hemoglobin level (g/dL)

5.3.3 Randomization Stratification Factors

Randomization stratification factors per IWRS recording will be summarized individually and as cross-tabulation:

- Presence of 17p del (yes, no)
- ECOG performance status (ECOG = 2 versus ECOG ≤1)
- Number of prior therapies (1-3 versus ≥ 4)

5.4 Medical History

General medical history data will be coded per Medical Dictionary for Regulatory Activities (MedDRA), summarized by system organ class and preferred term, and presented as a data listing.

6 TREATMENTS AND MEDICATIONS

Medications recorded on the electronic case report forms (eCRFs) will be coded using the World Health Organization (WHO) Drug Dictionary.

6.1 Prior and Concomitant Medications

Prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) Class text and WHO Drug base substance preferred name. Each subject will be counted only once for each therapeutic class, each generic name, and overall.

6.2 Prior and Subsequent Anticancer Therapies

Prior and subsequent anticancer therapy used to treat CLL will be coded and summarized based on line of therapy and type of therapy. Each subject will be counted only once for each line and type of therapy and overall.

6.3 Study Treatment Exposure

Study treatment exposure will be summarized by as follows:

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

6.4 Study Treatment Modifications

For subjects randomized to acalabrutinib arm, acalabrutinib dose withholding is defined as missing dose for ≥7 consecutive days, and acalabrutinib dose reduction is defined as taking lower dose level (100 mg QD) for ≥3 consecutive days. Subjects with dose withholding and reduction will be summarized by percent of subjects as well as descriptive statistics.

For subjects randomized to ibrutinib, dose delay and modifications are defined the same as acalabrutinib and will be summarized by percentage of subjects and by descriptive statistics.

7 EFFICACY ANALYSES

All efficacy analyses will be performed at the 2-sided significance level. Analyses will be based on the ITT population, and subjects will be analyzed according to the randomized treatment, unless otherwise specified.

The following three randomization stratification factors (collected via IWRS) will be used for the stratified analyses: presence of 17p del (yes, no), ECOG status (2 vs. ≤1), and number of prior therapies (1–3 vs. ≥4). For the primary efficacy analysis of IRC-assessed PFS, if there is at least one stratum that has fewer than 2 events (where a stratum is defined as stratification factor 1 * stratification factor 2 * stratification factor 3), stratification factors should be collapsed until all strata have at minimum 2 events for the primary endpoint. The stratification factors will be collapsed in the following order:

1. ECOG status (2 vs. ≤1)
2. Presence of 17p del (yes vs. no)

If there is still at least one stratum that has fewer than 2 events after collapsing the 2 stratification factors above, an unstratified analysis (equivalently as to collapse all 3 stratification factors) will be performed as the primary analysis.

All stratified analyses will be conducted in accordance with this prespecified pooling strategy as above stated for the primary analysis of PFS.

7.1 Primary Efficacy Endpoint and Analysis

7.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is PFS as assessed by IRC, defined as the time from date of randomization to the date of first IRC-assessed disease progression or death due to any cause.

Subjects who do not have an IRC confirmed disease progression or death at or prior to data analysis cutoff date will be censored as follows:

Table 2. Primary Efficacy Analysis of PFS-IRC Outcome

Situation	Date of Event or Censoring	Outcome
Situation 1: PFS events include death or first IRC-confirmed disease progression that occurred at or prior to the data analysis cutoff date. **Date of event is defined as follows:**		
Death before first disease assessment	Date of death	Event
IRC-confirmed PD or death between scheduled assessments	Earliest date of IRC confirmed PD or death	Event
Situation 2: All other cases not meeting Situation 1 will be censored as follows:		
No baseline assessments	Randomization	Censored
No adequate post-baseline assessment	Randomization	Censored
No IRC-confirmed PD or death at the time of data cutoff	Date of last adequate IRC assessment before data cutoff	Censored
No IRC-confirmed PD or death before lost to follow-up or study exit	Date of last adequate IRC assessment before lost to follow-up or study exit	Censored
No IRC-assessed PD or death before start of subsequent anticancer therapy	Date of the last adequate IRC assessment before start of subsequent anticancer therapy	Censored

Situation	Date of Event or Censoring	Outcome
IRC-assessed PD or death after start of subsequent anticancer therapy	Date of the last adequate IRC assessment before start of subsequent anticancer therapy	Censored
IRC-confirmed PD or death immediately after 2 or more consecutively missed visits	Date of last adequate IRC assessment before the consecutively missed visits	Censored

PD=progressive disease; IRC=independent review committee.

PFS will be calculated as date of disease progression or death (censoring date for censored subjects) – randomization date + 1.

The adequate IRC assessment is defined as the IRC-assessed overall response that is not 'UNK' (unknown), as defined in the IRC charter.

7.1.2 Primary Efficacy Analysis

The primary analysis, which is event-based, will be conducted after enrollment is completed and approximately 250 IRC events have been observed in the study. A summary of PFS events will be provided by treatment arm.

The estimate of the hazard ratio (acalabrutinib/ibrutinib) and its corresponding 95% CI will be computed using a Cox Proportional Hazards model stratified by the randomization stratification factors (collapsed if necessary, according to Section 7). Randomization stratification factors will be based on IWRS randomization assignment.

If the upper bound of the 2-sided 95% CI for the HR is below 1.429, acalabrutinib will be concluded to be non-inferior to ibrutinib.

Kaplan-Meier (KM) curves will be presented by treatment arm and the KM method will be used to estimate the distribution of PFS (quartiles and median with 95% CIs, minimum, and maximum). The proportion of subjects who are progression free and the corresponding 95% CI will be estimated based on KM method at select timepoints (e.g., 6, 12, 18, 24, 30, 36 months, etc.) by treatment arm.

7.1.3 Sensitivity Analyses

The following sensitivity analyses will be performed for PFS as assessed by IRC between acalabrutinib and ibrutinib in support of primary efficacy analyses:

- Unstratified analyses
- The PFS will be analyzed as the time from date of randomization to the date of first IRC-assessed disease progression or death due to any cause, whichever comes first, regardless of the use of subsequent anticancer therapy; i.e., subjects will not be censored at the last adequate IRC assessment prior to the subsequent anticancer therapy
- Subjects with PFS events after 2 or more consecutively missed visits will not be censored at the last adequate assessment. In particular, IRC-confirmed progressive disease or death after 2 or more consecutively missed visits will be included as a PFS event
- Analysis using per protocol population

7.1.4 Subgroup Analyses

Subgroup analyses will be performed using potential prognostic variables at screening or baseline listed below to investigate the consistency and robustness of the primary analysis:

- Randomization stratification factors per IWRS recording:
    - Presence of 17p deletion mutation (yes vs. no)
    - ECOG at randomization (0, 1 vs. 2)
    - Number of prior therapies (1-3 vs. ≥ 4; additionally, analyze 1, 2, 3, 4, ≥ 5 separately)
- Region (North America, Western Europe, Central and Eastern Europe, Asia Pacific)
- Age group (<65 vs. ≥65 years; <70 vs. ≥70 years; <75 vs. ≥75 years)
- Sex (male vs. female)
- Race (White vs. Non-White)
- Bulky disease (longest diameter of lymph node <5 cm vs. ≥5 cm or <10 cm vs. ≥10 cm at baseline)
- Rai Stage at screening (Stage 0-II vs. III-IV)
- Cytopenias at baseline (yes vs. no)

- Presence of 11q deletion mutation (yes vs. no)
- TP53 mutation (mutated vs. unmutated)
- IGHV (mutated vs. unmutated)
- Complex karyotype (yes vs. no)
- β_2-microglobulin at baseline (≤3.5 mg/L vs. >3.5 mg/L)
- High risk features:
    - 17p del and 11q del (yes, no)
    - 17p del and/or TP53 mutation (yes, no)
    - 17p del and TP53 mutation (yes, no)
    - 17p del and 11q del and TP53 mutation (yes, no)
    - 17p del and unmutated IGHV (yes, no)
    - 17p del and complex karyotype (yes, no)
    - 11q del and complex karyotype (yes, no)

The hazard ratio (Arm A/Arm B) and its corresponding 95% CI for each subgroup will be calculated based on an unstratified Cox regression model and displayed graphically in a forest plot.

Additional subgroups may be considered when appropriate.

7.2 Secondary Endpoints and Analyses

7.2.1 Grade ≥ 3 Infections, Richter's Transformation, and Atrial Fibrillation

Secondary endpoints related to safety will be analyzed using the safety population, and subjects will be analyzed as treated. If a subject incorrectly received both acalabrutinib and ibrutinib in any amount, the subject will be analyzed under the acalabrutinib arm.

The incidences of treatment emergent grade ≥ 3 infections, Richter's transformation, and atrial fibrillation will be summarized and compared between the 2 treatment arms using 2-sided Cochran-Mantel-Haenszel tests adjusted for the randomization strata (same strata used for the primary analysis of PFS based on the pre-specified pooling strategy).

Richter's transformation will be assessed by central pathology. Incidence of grade ≥ 3 infections and atrial fibrillation will be collected as described for all AEs and defined according to Appendix 1.

In addition, subgroup analyses will be performed for each endpoint using the subgroups listed in Section 7.1.4. For each endpoint, the risk difference (Arm A – Arm B) and its

corresponding 95% CI for each subgroup will be calculated based on normal approximation (with use of Wilson's score) and displayed graphically in a forest plot.

7.2.2 Overall Survival

OS will be analyzed using the ITT population and is defined as the time from date of randomization to date of death due to any cause. Subjects who were not known to have died prior to the analysis data cutoff date will be right-censored as follows:

Table 3. Overall Survival Censoring

Situation	Date of Event or Censoring	Outcome
Death before first disease assessment	Date of death	Event
Death between scheduled assessments	Date of death	Event
All other cases will be censored as follows:		
Lost to follow-up immediately after randomization	Randomization date	Censored
Not known to have died at or prior to analysis data cutoff date	Date last known alive before analysis data cutoff date	Censored
Not known to have died prior to lost to follow-up or study exit	Date last known alive before lost to follow-up or study exit	Censored

OS will be calculated as death date (or censoring date) - randomization date + 1.

OS will be analyzed in the same fashion as that for primary efficacy endpoint as described in Section 7.1.2. A stratified log rank test will be performed, adjusting for the randomization stratification factors used for the primary analysis.

Additionally, a subgroup analysis will be performed for OS in the same manner, and using the same subgroups, as described in Section 7.1.4.

7.3 Exploratory Efficacy Endpoints and Analyses

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7.3.1 CCI

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7.3.2 CCI

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7.3.3 CCI

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7.3.4 CCI

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7.3.7 CCI

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7.3.8 CCI

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7.3.9 Additional Exploratory Analyses

Additional exploratory analyses are described below. Further exploratory analyses may be conducted as appropriate.

7.3.9.1 CCI

CCI

8 SAFETY SUMMARIES

All safety analyses will be performed using the safety population, and subjects will be analyzed as treated. If a subject incorrectly received both acalabrutinib and ibrutinib in any amount, the subject will be analyzed under the acalabrutinib arm.

Safety and tolerability will be assessed by the incidence of treatment emergent adverse events (TEAEs), changes in laboratory parameters and vital signs from baseline, and ECOG performance score.

8.1 Adverse Events

Each adverse event terms recorded on the eCRF will be mapped to a preferred term and system organ class through use of the MedDRA. The severity of AEs will be graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03 or higher for hematologic and non-hematologic AEs. The investigator will judge each event to be “not related” or “related” to study treatment.

8.1.1 Treatment Emergent Adverse Events

TEAE is defined as an adverse event reported during the treatment emergent period (defined in Section 4.1.6). Any ongoing event that worsens in severity after the first dose date of study drug is also defined as a TEAE. Incomplete onset dates will be imputed as detailed in Section 4.2, for the purpose of determining whether AEs are treatment emergent.

TEAEs will be tabulated in summary tables by treatment arm. For each treatment arm, frequency and percentage of adverse events within each system organ class and preferred term will be presented. The denominator for the adverse event incidence will be based on the number of safety population subjects in that treatment arm, unless otherwise specified. Adverse event incidence rates will also be summarized by severity and relationship to study drug based on the investigator’s judgment.

Subjects with multiple occurrences of events for a given preferred term, system organ class, or overall will be counted only once at the maximum severity and strongest relationship to study drug, respectively, for each preferred term and system organ class.

In addition, Grade 3 or Grade 4 TEAEs, TEAEs that led to permanent study drug discontinuation, TEAEs that led to dose reduction, TEAEs that led to dose interruption, serious TEAEs, and TEAEs that resulted in death will be summarized by treatment arm as treated.

8.1.2 Adverse Events of Clinical Interest

Adverse events of clinical interest (ECIs) are specified in Appendix 1 and are to be reported for the duration of study treatment and during any protocol-specified follow-up periods, including post-disease progression phase for overall survival. These events will be summarized similarly to TEAEs by treatment arm.

8.1.3 Adverse Events of Special Interest

Adverse events of special interest (AESIs) differ from ECIs in that they must be reported to the sponsor expeditiously and are defined according to Appendix 1. AESIs will be summarized similarly to TEAEs by treatment arm.

8.1.4 Subgroup Analyses for Adverse Events

Subgroup analyses will be performed for TEAEs using the same subgroups used for the primary endpoint subgroup analyses (listed in Section 7.1.4) to investigate benefit:risk for acalabrutinib versus ibrutinib.

For each of the TEAE types listed below, the risk difference (Arm A – Arm B) and its corresponding 95% CI for each subgroup will be calculated based on normal approximation (with use of Wilson's score) and displayed graphically in a forest plot. Additional subgroups may be considered as appropriate.

- Grade ≥3 TEAEs
- TEAEs leading to dose interruption
- TEAEs leading to discontinuation of treatment

8.2 Deaths

All reported deaths will be summarized by treatment arm and cause of death. A by-subject listing that includes date of death and cause of death will be provided.

8.3 Laboratory Assessments

8.3.1 Data Processing Methods

All laboratory values will be converted to and reported as 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 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 with use of both 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 percentage 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 be counted only once for each criterion/direction. The same subject can be counted for both criteria if the subject has laboratory values that meet each criterion. Subjects who meet the criteria for Grade 1 or higher for the high direction will be summarized under Grade 0 for summarization of the low direction and vice versa. Change from baseline to post-baseline value will be calculated for each parameter.

8.3.2 Analysis of Treatment Emergent Clinical Laboratory

Subject incidence of hematologic toxicities for platelet counts, hemoglobin, and neutrophils, graded per IWCLL 2008 guideline and CTCAE, will be summarized by treatment arm and grade.

The treatment emergent laboratory abnormality is defined as laboratory abnormality reported during the treatment emergent period (defined in Section 6). Treatment emergent laboratory abnormality, per NCI CTCAE v4.03 grading, will be summarized for hematology and chemistry laboratory parameters of clinical interest.

Shift from baseline grade to maximum post-baseline CTCAE grade will be summarized for hematology and chemistry laboratory parameters of clinical interest.

8.3.3 Analysis of Lymphocytosis

For all subjects with baseline and any post-baseline absolute lymphocyte count (ALC) measurements, ALC at peak summary will be provided by treatment arm. Median percentage change in ALC from baseline with its 95% CI will also be displayed graphically over time.

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8.3.4 Analysis of Serum Immunoglobulins

Serum immunoglobulins (IgA, IgG, and IgM) will be summarized using descriptive statistics at each scheduled post-baseline time point. An additional IgG summary to exclude subjects who received IV immunoglobulin on the study will be provided.

8.4 ECOG Performance Status

The ECOG performance status grade ranges from 0 to 5. The ECOG performance score will be summarized by descriptive statistics. Shift to maximum post-baseline score in ECOG performance score will be summarized by treatment arms.

8.5 Vital Signs and Weight

Body temperature, pulse rate (beats/min), systolic and diastolic blood pressure (mmHg), respiratory rate (breaths/min), and weight (kg) will be summarized. Systolic and diastolic blood pressure will be graded using NCI CTCAE v4.03. Shift to maximum post-baseline score will be summarized for blood pressure parameters by treatment arms.

8.6 Electrocardiogram

Subject incidence of ECG abnormality at baseline and post-baseline visits will be summarized by treatment arms. Number and percentage of subject with QTcB or QTcF values >480 msec at screening visit will be summarized in a table.

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9.2.1 CCI

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9.2.2 CCI

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9.2.3 CCI

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9.2.4 CCI

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11 APPENDIX

APPENDIX 1 – Definition of Adverse Event of Special Interest and Events of Clinical Interest (MedDRA version 23.0)

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 haemorrhage

APPENDIX 2 – 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: ≥3×ULN AST or ≥3×ULN ALT and ≥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 23.0