Protocol Number: ACE-LY-003

Protocol Title: An Open-label, Phase 1b/2 Study of Acalabrutinib Alone or in Combination Therapy in Subjects with B-cell Non-Hodgkin Lymphoma

Version: 1.0

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The undersigned have reviewed this plan and find it to be consistent with the requirements of the protocol.

Prepared By:

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Approved By:

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Redacted for Public Disclosure

Statistical Analysis Plan (Parts 2-3 of Study ACE-LY-003)

An Open-label, Phase 1b/2 Study of Acalabrutinib Alone or in Combination Therapy in Subjects with B-cell Non-Hodgkin Lymphoma

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TABLE OF ABBREVIATIONS

AE	Adverse event
AESI	Adverse event of special interest
ATC	Anatomical therapeutic chemical
BID	Twice per day
BTK	Bruton's tyrosine kinase
COVID-19	Coronavirus disease 2019
CR	Complete response
CRF	Case report form
CSP	Clinical study protocol
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
DOR	Duration of response
ECI	Event of clinical interest
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
FLIPI	Follicular Lymphoma International Prognostic Index
FL	Follicular Lymphoma
GELF	The Groupe d'Etude des Lymphomes Folliculaires
IPD	Important protocol deviation
IV	Intravenous
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MZL	Marginal zone lymphoma
MRD	Minimum residual disease
ORR	Overall response rate
OS	Overall survival
PD	Pharmacodynamic / progressive disease
PFS	Progression-free survival
PK	Pharmacokinetic
PO	Orally

PR	Partial response
PT	Preferred term
QD	Once per day
R/R	Relapsed/refractory
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation / stable disease
SOC	System organ class
TEAE	Treatment-emergent adverse event
TTNT	Time-to-next treatment
ULN	Upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide detailed methodology for summary and statistical analyses of the safety and efficacy endpoints that have been outlined within Parts 2 and 3 of Clinical Study Protocol (CSP) Amendment 6 for Study ACE-LY-003, which is entitled "An Open-label, Phase 1b/2 Study of Acalabrutinib Alone or in Combination Therapy in Subjects with B-cell Non-Hodgkin Lymphoma" dated March 5, 2020. This SAP will be used to support a clinical study report (CSR).

2. OBJECTIVES

2.1 Part 2 (Marginal Zone Lymphoma)

2.1.1 Primary Objective

- To characterize the activity of acalabrutinib alone or in combination with rituximab in subjects with relapsed/refractory (R/R) marginal zone lymphoma (MZL), as measured by overall response rate (ORR)

2.1.2 Secondary Objectives

- To characterize the safety of acalabrutinib alone or in combination with rituximab in subjects with R/R MZL
- To evaluate the activity of acalabrutinib alone or in combination with rituximab in subjects with R/R MZL, as measured by duration of response (DOR), progression-free survival (PFS), and overall survival (OS)

2.1.3 Exploratory Objectives

- CCI

2.2 Part 3 (Follicular Lymphoma)

2.2.1 Primary Objective

- To characterize the safety of acalabrutinib in combination with rituximab and lenalidomide in subjects with R/R follicular lymphoma (FL)

2.2.2 Secondary Objectives

- To characterize the activity of acalabrutinib in combination with rituximab and lenalidomide in subjects with R/R FL as measured by ORR, DOR, PFS, and OS

2.2.3 Exploratory Objectives

- CCI

3. STUDY OVERVIEW

3.1 Study Design

Part 2

This part of the study is a Phase 2, multicenter, open-label, study to be conducted at approximately 38 centers. Up to 40 subjects with R/R MZL will be enrolled. At the time of CSP Amendment 6, the decision was made to close Cohort 2 (one subject was enrolled on Cohort 2).

- Cohort 1: Acalabrutinib 100 mg orally (PO) twice per day (BID) administered approximately 12 hours apart (BID dosing=200 mg total daily dose).
- Cohort 2: Acalabrutinib 100 mg PO BID administered approximately 12 hours apart (BID dosing=200 mg total daily dose), plus rituximab 375 mg/m2 intravenous (IV) on Days 1, 8, 15, and 22 of Cycle 1 and Day 1 of Cycles 2 through 6.

Part 3

This part of the study is a dose-finding, Phase 1b, multicenter, open-label study to be conducted at approximately 38 centers. Approximately 26 to 32 subjects with R/R FL will be enrolled and treated with acalabrutinib, rituximab, and lenalidomide. Once a safe and tolerable dose of lenalidomide has been established, 14 subjects (as part of the 26 to 32 subjects total) will be treated on the 3 drugs at that dose of lenalidomide.

- Acalabrutinib 100 mg PO BID administered approximately 12 hours apart (BID dosing=200

mg total daily dose), until disease progression or an unacceptable toxicity occurs.

- Rituximab 375 mg/m2 IV administered on Days 1, 8, 15, and 22 of Cycle 1, and Day 1 of every cycle starting at Cycle 2 through Cycle 6, followed by 10 additional doses of maintenance rituximab every other cycle beginning with Cycle 8 for subjects who have not progressed.
- Lenalidomide will start at 15 mg PO once per day (QD) for the first 6 subjects in Cycle 1. Doses up to 20 mg PO QD will be explored. Lenalidomide will be administered on Days 1 through 21 of a 28-day cycle.

Six subjects are planned to be enrolled initially and treated with acalabrutinib, rituximab, and lenalidomide (15 mg PO QD) in Cycle 1. At the end of the cycle, subjects will be evaluated for dose-limiting toxicities (DLTs) on a rolling basis.

- If there are ≥2 subjects with DLTs on 15 mg of lenalidomide QD, the dose of lenalidomide will be reduced to 10 mg QD, and 6 more subjects are planned to be enrolled at this reduced dose of lenalidomide.
    - If there are ≥2 subjects with DLTs at the end of Cycle 1 on 10 mg lenalidomide QD, enrollment will close.
    - If there are <2 of 6 subjects with DLTs, then approximately 14 additional subjects will be enrolled and treated with lenalidomide 10 mg QD for Cycles 1 through 12.
- If there are <2 of 6 subjects with DLTs on 15 mg QD, 6 additional subjects are planned to be enrolled to receive an increased dose of lenalidomide at 20 mg QD.
    - If there are ≥2 subjects with DLTs, the dose of lenalidomide will be reduced back to 15 mg QD. Approximately 14 more subjects will be added to complete enrollment at the 15-mg QD dose.
    - If there are <2 of 6 subjects with DLTs, 20 mg of lenalidomide will be the dose used for Cycles 2 through 12. Approximately 14 more subjects will be added to complete enrollment.

Note: Subjects will be evaluated for DLTs at the end of the first cycle, on a rolling basis, when they complete a cycle of treatment.

For both parts, twenty-eight days is one cycle. Treatment with acalabrutinib may be continued until confirmed disease progression or an unacceptable drug-related toxicity occurs. Please refer to CSP Appendices 5 and 6 for the complete schedule of assessments.

3.2 Sample Size

Part 2

Part 2 will enroll up to 40 subjects in Cohort 1 that will provide data for an initial assessment of safety and efficacy of acalabrutinib treatment. Sample size is not based on statistical power consideration. At the time of CSP Amendment 6, the decision was made to close Cohort 2 (per CSP Amendment 4, Cohorts 1 and 2 were planned to enroll 20 subjects each). One subject was enrolled in Cohort 2 before it was closed.

Part 3

A total of approximately 26 to 32 subjects are to be enrolled in Part 3. This sample size will provide adequate data for an initial assessment of safety and efficacy of acalabrutinib treatment in combination with lenalidomide and rituximab. This sample size is not based on statistical power consideration.

4. STUDY ENDPOINTS

4.1 Efficacy Endpoints

Standardized response and progression criteria have been established for lymphoma (Cheson et al. 2014); assessments of efficacy in this study will be based on these criteria. For Parts 2 and 3, the efficacy endpoints include:

- ORR
- DOR
- PFS
- OS
- CCI [redacted]

4.2 Safety Endpoints

The safety of acalabrutinib alone, or in combination with rituximab, or in combination with rituximab and lenalidomide, will be characterized by adverse event (AE) type, frequency, severity, timing of onset, duration, and relationship to study drug (acalabrutinib, rituximab, and/or lenalidomide); serious adverse events (SAEs); and AEs leading to dose interruption of rituximab, reduction of acalabrutinib and/or lenalidomide, or withholding or discontinuation of acalabrutinib, lenalidomide, and/or rituximab.

For consistency of interpretation, AEs will be coded using Medical Dictionary for Regulatory

Activities (MedDRA), and the severity of AEs and laboratory abnormalities will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Standard definitions for seriousness will be applied (see CSP Section 6.2).

4.3 Pharmacokinetic (PK) and Pharmacodynamic (PD) Parameters

Part 2

No PK analysis will be performed in Part 2. The PD analyses will be detailed in a separate analysis plan: the effect of acalabrutinib on biologic markers of BTK function will be evaluated; molecular profiling of tumor, blood, and bone marrow, when available (including but not limited to BTK mutation), will be performed.

Part 3

Sparse acalabrutinib PK samples will be collected and analyzed to investigate the relationship between acalabrutinib and its active metabolite (ACP-5862) concentration and response. The PD analyses will be detailed in a separate analysis plan: the effect of acalabrutinib on biologic markers of BTK function will be evaluated; molecular profiling of tumor, blood, ctDNA, and bone marrow when available (including but not limited to BTK mutation), will be performed.

5. ANALYSIS POPULATIONS

5.1 All-Treated Population

The all-treated population is defined as all subjects who receive ≥1 dose of any study drug (acalabrutinib, rituximab, or lenalidomide). Demographic and baseline characteristics, efficacy analyses, and safety analyses will be performed on the all-treated population unless otherwise specified.

5.2 Efficacy-Evaluable Population

The efficacy-evaluable population will include all subjects in the all-treated population who have ≥1 response assessment after the first dose of any study drug (i.e. overall response not “unknown” or missing). Sensitivity analyses for efficacy will be carried out on the efficacy-evaluable population.

5.3 PK Population

The PK population will be defined for Part 3 only and will include all subjects who receive ≥1 dose

of acalabrutinib and have ≥1 PK measurement after the first dose of acalabrutinib. PK analyses will be carried out on the PK population.

6. GENERAL CONVENTIONS

Part 2 and Part 3 analyses will be performed separately. Unless otherwise specified, the analyses outlined in this SAP will be performed for both Part 2 and Part 3.

Continuous data will be summarized using descriptive statistics (number of observations, mean, standard deviation, median, minimum, and maximum). Frequencies and percentages will be used for summarizing categorical data. Confidence intervals, when presented, will generally be constructed at the 2-sided 95% level. For binomial variables, the exact method 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 and total unless otherwise specified. Data will be presented in data listings by treatment arm and subject number.

6.1 Definitions

6.1.1 Definition of Baseline and Post-Baseline Value

Baseline is defined as the last measurement taken prior to the first dose of any study drug. A post-baseline value is defined as a measurement taken after the first dose of any 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.

6.1.2 Definition of Study Day

Study Day 1 is defined as the first dose date of any study drug. For visits (or events) that occur on or after first dose date, study day is defined as (date of visit [event] – first dose date + 1). For visits (or events) that occur prior to first dose date, study day is defined as (date of visit [event] – first dose date).

6.1.3 Definition of Prior and Concomitant Medication

For the purpose of inclusion in prior and/or concomitant medication summaries, incomplete medication start and stop dates will be imputed as detailed in Section 6.2. Based on imputed start and stop dates:

- Prior medications are defined as medications with a start date occurring before the date of first dose of any study drug.
- Concomitant medications are defined as medications that:
    - Had start date on or after the first dose date of study drug and either within 30 days after the last dose date (latest of any study drug), or before the first dose date of subsequent anticancer therapy, whichever is earlier, or
    - Had start date before first dose date of any study drug and were either ongoing or had a stop date on or after first dose date.
- Medications that meet the criteria for both prior and concomitant medication will be classified as both prior and concomitant medication.
- Medications with completely missing start and stop dates will be considered as both prior and concomitant medications.

6.1.4 Prior and Subsequent Anticancer Therapy

For the purpose of inclusion in the prior and/or subsequent anticancer therapy summaries, incomplete medication start dates will be imputed as detailed in Section 6.2. Based on imputed start dates:

- Prior anticancer therapies are defined as therapies with a start date before the date of first dose date of any study drug.
- Subsequent anticancer therapies are defined as therapies with a start date after the date of last dose (latest of any study drug).

6.1.5 Treatment Emergent Period

The treatment emergent period is defined as the period of time from the date of the first dose of any study drug through either 30 days after the date of the last dose (latest of any study drug) or the first date of subsequent anticancer therapy, whichever is earlier.

6.2 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.

6.2.1 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 imputed date for initial diagnosis or prior anticancer therapy is on or after date of first dose date of any study drug, then date of first dose – 1 will be used. If such imputed date for subsequent anticancer therapy is before date of last dose (latest of any study drug), 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 of any study drug, 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 (latest of any study drug) + 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.

6.2.2 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's survival time.

6.2.3 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.

6.2.4 Laboratory Values Below/Above the Level of Quantification

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.

6.2.5 PK Sample Dates

Missing dates or times may be imputed for PK samples if the missing values can be established with an acceptable level of accuracy based on other information obtained during the visit in question.

6.3 Software

Statistical analyses and data summary will be conducted using SAS Version 9.4 or higher.

7. STATISTICAL METHODS OF ANALYSIS

7.1 Subject Disposition

Enrollment for subjects in the all-treated population will be presented by region, country, and site. Subject disposition will be summarized including the following information:

- Subject status on each assigned study drug (acalabrutinib, rituximab, and/or lenalidomide)
- Primary reason for each study drug discontinuation
- Subject status on the study
- Primary reason for study exit
- Time on the study (months): (earlier of study exit date or data cutoff date – first dose date of any study drug + 1)/30.4375

7.2 Important Protocol Deviations

Number and percentage of subjects with important protocol deviations (IPDs) will be summarized, and 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.

7.3 Baseline Data

The following demographics and baseline characteristics will be presented.

7.3.1 Demographics

- Age (continuous)
- Age group (<60 versus ≥60 years; <65 versus ≥65 years; <75 versus ≥75 years)
- Sex (male, female)
- Race
- Ethnicity
- Region

7.3.2 Baseline and Disease Characteristics

- Eastern Cooperative Oncology Group (ECOG) performance score (0, 1, or 2)
- Height (cm)
- Weight (kg)
- Time from initial diagnosis to first dose of any study drug (months)
- Number of prior systemic regimens (excludes maintenance, consolidation, adjuvant, and neoadjuvant therapies when reported on the case report form [CRF] as a separate record)
    - Number of regimens (mean, standard deviation [SD], median, minimum, maximum)
    - Regimen group (1, 2, 3, 4, ≥5)
- Time from end of last prior treatment to first dose of any study drug
    - Time (mean, SD, median, minimum, maximum)
    - Time group (≤2 years, >2 years)
- Stem cell transplant (Yes)
- Baseline B symptoms
    - Any B symptom
        - Unintentional weight loss
        - Fever over 38 °C
        - Night sweats
- Bulky disease, defined as longest diameter of any target lesion at baseline
    - <5 cm
    - ≥5 cm and <10 cm
    - ≥10 cm
- Ann Arbor stage at study entry (Stage I, I-E, II, II-E, III, IV; Stage I-II, III-IV)
- Bone marrow involvement
- Lactate dehydrogenase (LDH; ≤ upper limit of normal [ULN], > ULN to 3x ULN, or ≥ 3x ULN; > ULN)
- Refractory vs relapsed to last treatment
    - Refractory is defined as best response of stable disease (SD), or progressive disease (PD), or a partial response (PR)/CR with DOR ≤6 months
    - Relapsed is defined as best response of PR/CR with DOR >6 months
- Part 2 only:
    - MZL subtype (Extranodal [Gastric MALT or Non-Gastric MALT], Nodal, Splenic)
- Part 3 only:
    - FL Grading (Grade 1, 2, or 3a)

- Extranodal disease (yes, no), defined as extranodal notations other than “spleen”
- Follicular Lymphoma International Prognostic Index score (FLIPI; Federico 2009) , defined as the number of following factors which are true: age > 60, Ann Arbor stage ≥ 3, hemoglobin < 12 g/dL, concentration of serum LDH > ULN, number of nodal areas ≥ 4.
  - Low (score 0-1)
  - Intermediate (score 2)
  - High (score 3-5)
- High tumor burden (yes, no) per The Groupe d’Etude des Lymphomes Folliculaires (GELF) Criteria, defined as at least one of the following: a target lesion >7 cm in diameter, three nodal target lesions >3 cm in diameter each, any B symptom, concentration of serum LDH > ULN, concentration of serum hemoglobin ≤100 g/L, neutrophil count ≤1500 cells per µL, platelet count ≤100,000 platelets per mL
- Refractory to any prior regimen containing anti-CD20 antibodies (yes, no); refractory is defined as best response of SD, or PD, or a PR/CR with DOR ≤6 months
- Double refractory (yes, no), defined as refractory to any prior regimen containing anti-CD20 antibodies and refractory to a prior alkylating agent-containing therapy, either in separate regimens or in the same regimen

Additional baseline characteristics may be summarized as appropriate.

7.3.3 Medical History

General medical history data will be coded per MedDRA, summarized by system organ class (SOC) and preferred term (PT), and presented as a data listing (including CTCAE severity grade).

7.5 Treatment and Medications

7.5.1 Prior and Subsequent Anticancer Therapies

Prior and subsequent anticancer therapy is defined in Section 6.1.4. Number and percentage of subjects taking each prior and subsequent anticancer therapy will be summarized by type of therapy.

7.5.2 Prior and Concomitant Medications

Prior and concomitant medications are defined in Section 6.1.3. Prior and concomitant medications will be coded by the World Health Organization (WHO) Drug Dictionary and summarized by Anatomic Therapeutic Chemical (ATC) Classification level 2 and PT.

7.5.3 Exposure to Study Drug

Descriptive statistics will be used to summarize for acalabrutinib:

- Duration of exposure (months): (last dose date – first dose date +1) / 30.4375
- Actual cumulative dose (g)
- Average daily dose (mg): (actual cumulative dose [mg]) / (duration of exposure [days])
- Relative dose intensity (RDI): (actual cumulative dose [mg]) / (duration of exposure [days] * 100 [mg] * 2) *100

Acalabrutinib dose withholding and reduction is based on the data from the dose administration CRF. The reasons for acalabrutinib dose withholding and reduction will be summarized.

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

Total exposure to rituximab will be summarized by descriptive statistics by each treatment time point, i.e. Day 1, 8, 15, and 22 of Cycle 1, and Day 1 of Cycles 2-6. For Part 3, subjects who have not progressed will received 10 additional doses of maintenance rituximab, every other cycle beginning with Cycle 8 (until Cycle 26, disease progression, or intolerance). Actual Dose administered is reported in mg. Rituximab dose reduction and interruption is based on the data from the dose administration CRF. The reasons for rituximab dose reduction and interruption will be summarized.

Descriptive statistics will be used to summarize for lenalidomide:

- Duration of exposure (months): (last dose date – first dose date + 1) / 30.4375
- Actual cumulative dose (g)
- Average daily dose based on 21 days of 28 day cycle (mg): (actual cumulative dose [mg]) / (number of planned lenalidomide dosing days [per CSP, first 21 days of each cycle] between subject's first and last dose of lenalidomide).
    - Number of planned lenalidomide dosing days can be calculated as: (duration of exposure [days]) - 7*(number of cycles subject took any lenalidomide - 1 cycle).
    - Number of cycles subject took any lenalidomide can be calculated as: (duration of exposure [days]/28), rounded up to the nearest integer.

- RDI: (average daily dose [mg]) / (assigned daily dose [15 or 20 mg])*100

Lenalidomide dose withholding and reduction is based on the dose administration CRF. The reasons for lenalidomide dose withholding and reduction will be summarized.

- Dose withholding of lenalidomide is defined as missing dose for ≥7 consecutive days (days 22-28 of each cycle are not considered as they are not dosing days).
- Dose reduction is defined as taking lower than assigned dose level of lenalidomide for ≥3 consecutive days (days 22-28 of each cycle are not considered as they are not dosing days).

Missing exposure data (e.g., the subject does not provide the dosing log for a certain time period) will be considered as dose of 0 mg for the calculation of summary statistics.

7.6 Analyses of Efficacy Endpoints

Efficacy analyses will be performed on the all-treated population. Sensitivity analyses may be performed based on the efficacy-evaluable population.

7.6.1 Overall Response Rate

Best overall response is defined as the best disease outcome over all response assessments on or before the initiation of subsequent anticancer therapy. Best overall response categories include CR, PR, SD, and PD. The number and percentage of subjects in each best overall assessment category will be presented by treatment arm. ORR will be defined as the proportion of subjects who achieve a CR or PR according to the Lugano Classification for NHL (Cheson et al. 2014), as assessed by investigators. ORR will be calculated, and the corresponding 2-sided 95% confidence interval will be derived.

7.6.2 Duration of Response

The DOR is defined as the interval from the first documentation of CR or PR to the earlier of the first documentation of definitive disease progression or death from any cause. Following first documentation of CR or PR, subjects who do not experience a disease progression or death will be censored using the same rule for PFS as described in Table 1. DOR is calculated as date of disease progression or death (censoring date for censored subjects) – date of achieving the first CR, CRi, PR, or nPR + 1. Kaplan-Meier (KM) methods similar to those described in Section 7.6.3 will be used to estimate event-free curves and corresponding quantiles (including the median) by

arm.

If at least 1 responder has an event of death (and without progression prior to death) due to Coronavirus disease 2019 (COVID-19), a sensitivity analysis will be conducted to assess for the potential impact of deaths due to COVID-19. Subjects with death related to COVID-19 infection (and without progression prior to death) will be censored at their last evaluable assessment prior to their COVID-19 related death date.

7.6.3 Progression-Free Survival

PFS is defined as the interval from the first dose date of any study drug to the earlier of the first documentation of objective disease progression or death from any cause.
Subjects who do not have disease progression or death at or prior to data analysis cutoff date will be censored according to Table 1.

Table 1. PFS Censoring

Situation	Date of Event or Censoring	Outcome
Situation 1: PFS events include death or first disease progression as assessed by investigator that occurred at or prior to the earliest of data analysis cutoff date, alternative cancer therapy start date, and discontinuation from study (and not immediately following ≥2 consecutively missed visits where CT scan was required). Date of event is defined as follows:		
Death before first disease assessment	Date of death	Event
INV-PD or death before study exit or data cutoff	Earlier date of INV-PD or death	Event
Situation 2: All other cases not meeting 'Situation 1' will be censored as follows:		
No baseline assessment	First dose date of any study drug	Censored
No adequate* post-baseline assessment	First dose date of any study drug	Censored
No INV-PD or death at the time of data cutoff	Date of last adequate* INV assessment before data cutoff	Censored
No INV-PD or death before lost to follow-up or study exit	Date of last adequate* INV assessment before lost to follow-up or study exit	Censored

No INV-PD or death before start of subsequent anticancer therapy	Date of last adequate* INV assessment before start of subsequent anticancer therapy	Censored
INV-PD or death immediately after two or more consecutively missed visits (where CT scan was required)	Date of last adequate* INV assessment before missing two or more consecutive visits	Censored

Abbreviation: INV=investigator

*Assessment is adequate if it is not "Unknown/NA" or missing

PFS will be calculated as date of disease progression or death (censoring date for censored subjects) – date of first dose of any study drug + 1.

Kaplan-Meier methods will be used to estimate the event-free curves by arm and corresponding quantiles (including the median). The proportion of subjects who are progression-free and the corresponding 95% CI will be estimated based on KM method at select timepoints by treatment arm.

If at least 1 subject has an event of death (and without progression prior to death) due to COVID-19, a sensitivity analysis will be conducted to assess for the potential impact of deaths due to COVID-19. Subjects with death related to COVID-19 infection (and without progression prior to death) will be censored at their last evaluable assessment prior to their COVID-19 related death date.

7.6.4 Overall Survival

The duration of OS will be measured from the first dose date of any study drug until the date of death due to any cause. Subjects who were not known to have died prior to the analysis data cutoff date will be censored as detailed in Table 2.

Table 2. 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
Known to have died, but death date is missing month and day or is completely unknown	Date last known alive before death	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) – first dose date of any study drug + 1.

OS will be analyzed in the same fashion as that for primary efficacy endpoint as described for PFS in Section 7.6.3.

If at least 1 subject has an event of death due to COVID-19, a sensitivity analysis will be conducted to assess for the potential impact of deaths due to COVID-19. Subjects with death related to COVID-19 infection will be censored at their date of death due to COVID-19.

7.6.5 Time-to-Next Treatment

CCI [redacted]

7.7 Analyses of Safety Endpoints

Safety analyses will be performed by treatment arm on the all-treated population.

Analyses of AEs will be performed on treatment-emergent AE (TEAE) data, unless otherwise specified. TEAEs are defined as those adverse events with onset or worsen date during the treatment emergent period, which is defined in Section 6.1.6. All AE terms will be coded by

MedDRA, and severity will be graded per CTCAE version 5.0.

7.7.1 Adverse Events

Subject incidence of the following events will be tabulated by SOC and/or PT in descending order of frequency. Summaries will also be presented by the severity of the AE and by causality of study drug(s).

- TEAEs
- SAEs
- TEAEs related to study drug(s)
- SAEs related to study drug(s)
- TEAEs leading to study drug(s) discontinuation, dose modification, and delay
- Confirmed or suspected COVID-19 TEAEs
- Confirmed or suspected COVID-19 AEs (including those that are not treatment-emergent)
- COVID-19 associated TEAEs
- COVID-19 TEAEs leading to death

COVID-19 associated AEs are defined as all confirmed and suspected COVID-19 AEs, plus all other AEs occurring within <7 days before and <30 days after the start date of all the confirmed COVID-19 AEs

Summary tables and a listing will be provided when death is reported.

7.7.2 Adverse Events of Special Interest (AESIs) and Events of Clinical Interest (ECIs)

AESIs and ECIs are defined in Appendix 1. Subject incidence will be presented by treatment arm in the summary tables.

7.7.3 Laboratory Test Results

This study will primarily use central laboratory testing for laboratory evaluations. Samples from local laboratories will be used if central testing is unavailable. Analyses will be performed for laboratory test data collected at baseline and from first exposure to any study drug to 30 days after last dose (latest of any study drug) or up to the safety follow-up visit date, whichever is later. For hematology, serum chemistry, and T/8/NK cell count performed in the central laboratory, reference range and the results will be reported in standard international units. Generic normal ranges

(JAMA 2016) will be applied whenever reference ranges are not available (e.g., local laboratory data). Applicable laboratory test abnormalites will be graded according to CTCAE version 5.0.

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 maximum grade from first exposure to any study drug to 30 days after last dose (latest of any study drug) or up to the safety follow-up visit date, whichever is later, will be provided as shift tables for selected parameters.

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

7.7.4 Vital Signs

Analyses will be performed for vital sign safety data collected at baseline and from first exposure to any study drug to 30 days after last dose (latest of any study drug) 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 order to be included in the table, a subject must have at least one post-baseline value for the given time point.

7.7.5 ECOG Performance Score

Change of ECOG score from baseline to the maximum score during the period from first exposure to any study drug to 30 days after last dose (latest of any study drug) or up to the safety follow-up visit date, whichever is later, will be provided as shift tables.

7.7.6 Electrocardiogram (ECG)

Baseline in QT, heart rate, QTcB, QTcF, PR, RR, and QRS will be summarized by abnormality and clinical significance using Sponsor reporting standards. Listings of subjects with any single value

>480 msec will also be produced for QTcF and QTcB.

7.8 PK Parameters

For Part 2, no PK sample was collected. Therefore, there will be no PK analysis for Part 2.

For Part 3, plasma concentrations of acalabrutinib and ACP-5862 will be tabulated for each subject by arm, visit, and timepoint. Descriptive statistics (n, mean, standard deviation, %CV, median, minimum, maximum) of plasma concentrations of acalabrutinib (and metabolite(s), if applicable) will be presented by visit.

A by-subject listing of plasma concentrations will be provided. This listing will include: subject identifier, visit, unique sample ID, planned time post dose, actual time post dose and concentration.

8. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

In the definition for the efficacy-evaluable population, it was further specified that the ≥1 response assessment (as required per CSP Section 5.3) must have overall response not "unknown" or missing.

CSP Section 5.5.4 specifies that PFS, TTNT, and OS will be calculated using the first dose date of acalabrutinib as the reference date for time to event. However, as this study includes combination therapy, SAP Sections 7.6.3-7.6.5 were changed to specify that the date of first dose of any study drug will be used as the reference date for time to event.

9. AD HOC ANALYSES

In addition to the analyses described in earlier sections for the CSR, the following ad hoc analyses are planned to support the reporting of results in a manuscript and/or congress presentation(s). Further ad hoc analyses may be conducted as needed.

9.1 Ad Hoc Analyses for Part 2 (MZL)

9.1.1 Subgroup Analyses for ORR

A subgroup analysis will be performed for ORR in which the number and percentage of subjects in each best overall assessment category will be presented by treatment arm and MZL subtype.

Additionally, ORR and the corresponding 2-sided 95% confidence interval will be calculated for each subgroup listed below and displayed in a forest plot, following the method described in Section 7.6.1:

- MZL subtype
- Age group
- ECOG performance score
- Bulky disease
- Bone marrow involvement
- Number of prior systemic regimens
- Type of prior anticancer therapy

The subgroup analyses will be performed in both the all-treated population and the efficacy-evaluable population.

9.1.2 Swimmer Plot for Overall Response

A swimmer plot will be generated for time from first dose of any study drug to each overall response (CR, PR, SD, or PD). MZL subtype will be indicated for each subject on the plot. Death and treatment status on acalabrutinib will be shown (ongoing on acalabrutinib or discontinued acalabrutinib, with reason for discontinuation).

9.2 Ad Hoc Analyses for Part 3 (FL)

Subgroup analyses will be performed for the efficacy endpoints ORR, DOR, and PFS. The analyses described in Sections 7.6.1-7.6.3 (with exception of COVID-19 sensitivity analyses) will be repeated in the following subgroups:

- Refractory to any prior regimen containing anti-CD20 antibodies (yes)
- Double refractory (yes)

Additionally, ORR, median DOR, median PFS and the corresponding 2-sided 95% confidence intervals will be calculated for each subgroup listed below and displayed in forest plots, following the methods described in Sections 7.6.1-7.6.3:

- Ann Arbor stage at study entry
- Age group
- ECOG performance score
- Bulky disease

- Bone marrow involvement
- Number of prior systemic regimens
- Type of prior anti-cancer therapy
- FLIPI score
- High tumor burden per GELF criteria
- Refractory versus relapsed
- Refractory to any prior regimen containing anti-CD20 antibodies
- Double refractory

The subgroup analyses will be performed in the all-treated population and may be performed in the efficacy-evaluable population.

10. LITERATURE CITATIONS/ REFERENCES

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11. APPENDICES

APPENDIX 1 – Definition of Adverse Event of Special Interest and Events of Clinical Interest

The below definitions are based on MedDRA version 24.1 and will be updated as appropriate based on the most current MedDRA version used at the time of the data extract.

1. Adverse Event of Special Interest (AESI)

AESI Category	Definition
Ventricular arrhythmias	• PT Torsade de pointes • PT Ventricular arrhythmia • PT Ventricular extrasystoles • PT Ventricular fibrillation • PT Ventricular flutter • PT Ventricular tachyarrhythmia • PT Ventricular tachycardia
Suspected transmission of an infectious agent via product*	• PT Product cleaning inadequate • PT Product contamination • PT Product contamination chemical • PT Product contamination microbial • PT product sterility lacking • PT Transmission of an infectious agent via product • PT Suspected product contamination

*For subjects taking study treatment containing biologic products, e.g. rituximab.

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 arrhythmia • PT Ventricular extrasystoles • 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 Granulocyte count decreased • PT Granulocyte percentage decreased • 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 Query.

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
- Extraischaemic cerebral 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 apoplexy
- 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
- Vertebral artery perforation

APPENDIX 2 – Search Strategy for Narratives

1. **Primary Criteria for Narratives:**

   - All deaths (regardless of cause), other non-fatal 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 or start of new anticancer therapy, whichever comes first. Beyond this window, narratives should only 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 • Grade 4 non-serious hepatotoxicity
Second primary malignancies	Second primary malignancies (excluding non melanoma skin)	Below SMQs excluding PTs mapping to HLT Skin neoplasms malignant and unspecified (excluding melanoma) • SMQ Malignant tumours (including Haematological malignant tumours SMQ and Non- haemoatological malignant tumours SMQ • SMQ Malignant lymphomas [narrow] • SMQ Myelodysplastic syndrome [narrow]
Tumor lysis syndrome		Same as ECI definition. Refer to Appendix 1 Section 2

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; HLT=high-level term; ISS=integrated safety summary; PT=preferred term; SAE=serious adverse event; SMQ=Standardised MedDRA Query; ULN=upper limit of normal.
MedDRA version 24.1

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