

**A Phase 3b, Multicenter, Open-Label, Single-Arm Study of
Acalabrutinib (ACP-196) in Subjects with Chronic
Lymphocytic Leukemia**

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AMENDMENT HISTORY

Date	Brief description of change
19 Jun 2019	Final version
14 Oct 2019	SAP amendment v1.2 following the clinical study protocol amendment. • CCI [REDACTED] • Changed the sample size for the prior BTKi therapy cohort from ‘up to 70’ to ‘approximately 70 to 100’ participants • Added adverse event of special interest to the safety assessments • Added second primary malignancies to the list of events of clinical interest • Modified treatment-free survival to event-free survival • Added an exploratory objective to characterize the pharmacokinetics of study drug, and added the definition of PKAS • Updated Schedule of Assessments in the Appendix 1 based on the protocol amendment
7 Nov 2019	SAP amendment v1.3 following the sponsor’s comments. • Modified event-free survival to ‘time to next signs or symptoms of disease progression’
5 Mar 2020	SAP amendment v1.4 following the sponsor’s comments. • Added a fuller explanation of the cohorts in the Section 1.2 • Renamed the analysis sets by using CDISC-recognised names • Patient-Reported Outcome Analysis Set (PROAS) was added into analysis populations for participants in the SAF who have baseline and at least one post-baseline PRO assessment. The PRO analyses will be conducted on the PROAS. • Added 3 general categories of important protocol deviations in the Section 2.2 • Added detailed category of EORTC-QLQ-C30 in the Section 3.2.6.1 • Missing AE relatedness will be assumed to be related, added in the Section 4.1.3 • Summary table for Medical History was added in the Section 4.2.5 • Summary table for potential Hy’s law was added in the Section 4.3.4
21 Apr 2021	SAP amendment v1.5 following the sponsor’s comments and feedback received during dry run outputs review. • Removed PROAS and FAS from population in the Section 2.1. Efficacy analysis (including ePRO data) will be performed based on the SAF. • Updated category 4 for the definition of important protocol deviation in the Section 2.2 • Added censoring rule for PFS in the Section 3.2.3 for patients who are progression-free but do not have any post-baseline tumor assessment • Corrected question number used in the Section 3.2.6.1 • Removed ‘clinically meaningful major haemorrhage’ from Section 4.3.2, based on the protocol amendment • Removed chloride and total protein from CTC tables in the Section 4.3.3, as these two lab tests do not have corresponding CTC grade in the CTCAE v5.0.

Date	Brief description of change
18 Nov 2022	SAP amendment v1.6 following CSP amendment.
29 Nov 2022	SAP amendment v1.7 following the sponsor's comments. - Figures and tables updated according to CSP version 1.0 (Global) - SoA updated according to CSP version 1.0 (Global) - Details about ECIs and AESIs updated according to CSP version 1.0 (Global) - List of abbreviations updated - Definition of ORR added
1 Dec 2022	SAP amendment v1.8 following the sponsor's comments. - Section 6 updated, stating that there is no change of analysis from CSP - Concomitant medications and procedures recording period updated according to CSP.
10 May 2023	SAP amendment v2.1 following the sponsor's comments. Updated AESI and ECI categories for acalabrutinib
19 Jan 2024	SAP amendment v3.1 following protocol amendment 4. - Updated to accommodate required changes with protocol amendment 4, Version 5.0 (Global), 25 August 2023, mainly: - Updated to accommodate required changes with Acalabrutinib_PSSR_v1.0_Final_11Mar2024 - CCI - Study and design section has been adjusted with wordings. - Analysis data sets (SAF, PKAS) have been re-defined as required. - PFS censoring criteria have been elaborated and described as required. - Section 2.2 Protocol Deviations has been updated for Inclusion Criterion 4. - Appendix 1, Schedule of Assessments has been updated. - Appendix 2, Section II ECIs has been updated.
11 Aug 2025	SAP Amendment v4.1 After dry run 1 - Text added to align with the shells - COVID-19 text added for repeated outputs - Demographics to be presented on the PK analysis set - Added text about presenting nicotine use - Surgical history explicitly mentioned - ECOG explicitly mentioned - Discontinued subjects, screen failures, baseline characteristics, surgical history, efficacy response data, lab and lymphocytosis listings explicitly mentioned - Updates as result of AZ dry run 1 comments - Covariance structure added

Date	Brief description of change
21 Nov 2025	SAP Amendment v4.4 following sponsor's comments and dry run 2 • CCI [REDACTED] • Updated ECI major haemorrhage categories to align with PSSR v5

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACP-196	acalabrutinib
AE	adverse event
AESI	adverse event of special interest
ALC	absolute lymphocyte count
ALT	alanine aminotransaminase
ANC	absolute neutrophil count
Anti-HBc	hepatitis B core antibody
Anti-HBs	hepatitis B surface antibody
AST	aspartate aminotransaminase
bid	twice daily
BLQ	below the limit of quantification
BM	bone marrow
BMI	body mass index
BTK	bruton tyrosine kinase
BTKi	bruton tyrosine kinase inhibitor
°C	celsius degrees
CD	cluster of differentiation
CI	confidence interval
CIRS	cumulative illness rating scale
CLL	chronic lymphocytic leukemia
COVID-19	coronavirus disease 2019
CNS	central nervous system
CR	complete response
CRF	case report form
CRi	complete response with incomplete marrow recovery
CSP	clinical study protocol
CSR	clinical study report
CT	computed tomography
CTC	common toxicity criteria
CTCAE	common terminology criteria for adverse events
CV	coefficient of variation
CYP	cytochrome P450
d	actual cumulative dose delivered
D	intended cumulative dose

Abbreviation or special term	Explanation
DCO	data cut-off
Del(17p)	17p deletion
DOR	duration of response
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
EDTA	ethylene diamine tetra-acetic acid
eCRF	electronic case report form
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
°F	fahrenheit degrees
FISH	fluorescence in situ hybridization
HLT	high level term
HBsAg	hepatitis B surface antigen
HRQoL	health-related quality of life
G-CSF	granulocyte colony-stimulating factor
ICF	informed consent form
ICH	International Conference on Harmonization
ID	identification number
Ig	immunoglobulin
IGHV	immunoglobulin heavy-chain variable
IPD	important protocol deviation
IVIG	intravenous immunoglobulins
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
KM	kaplan-meier
LDH	lactate dehydrogenase
LDT	lymphocyte doubling time
LLQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MRI	magnetic resonance imaging
NCI	national cancer institute
NGS	next-generation sequencing
NK	natural killer
OR	overall response
ORR	overall response rate

Abbreviation or special term	Explanation
CCI	CCI
PCR	polymerase chain reaction
PET-CT	positron emission tomography-computed tomography
PFS	progression free survival
PK	pharmacokinetic
PKAS	pharmacokinetic analysis set
PO	per os (by mouth)
PR	partial response
PRO	patient-reported outcomes
PRO-CTCAE	patient-reported outcomes version of the common terminology criteria for adverse events
PT	preferred term
Q1	first quartile
q12w	every 12 weeks
q24w	every 24 weeks
Q3	third quartile
QoL	quality of life
QTcF	corrected QT interval using Fridericia's formula
RDI	relative dose intensity
R/R	relapsed/refractory
RS	raw score
SAE	serious adverse event
SAF	safety analysis set
SD	standard deviation
SI	standard international
SMQ	Standardized MedDRA Queries
SFU	safety follow-up
SoA	schedule of assessments
SOC	system organ class
TBILI	total bilirubin
TEAE	treatment-emergent adverse event
TN	treatment-naïve
CCI	CCI
ULN	upper limit of normal
WHODrug	World Health Organization Drug Dictionary

STUDY DETAILS

1.1 Study Objectives

1.1.1 Primary Objective

Primary objective	Endpoints
To evaluate the safety and tolerability of acalabrutinib monotherapy in participants with treatment-naïve (TN) or relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL)	Frequency, severity and relatedness of all adverse events (AEs), which will also include: - Grade ≥ 3 AEs - Serious adverse events (SAEs) - Adverse event of special interest (AESI) defined as ventricular arrhythmias - AEs that lead to discontinuation of treatment - Events of special interest (ECIs) defined as cardiac events, hepatotoxicity, hypertension, infections, interstitial lung disease/pneumonitis, hemorrhage (major hemorrhage), cytopenias (anemia, leukopenia, thrombocytopenia), second primary malignancies, and tumor lysis syndrome.

1.1.2 Secondary Objective

Secondary objective	Endpoints
To evaluate the investigator-assessed overall response (OR), duration of response (DOR), and progression-free survival (PFS) in participants receiving acalabrutinib monotherapy	- OR - DOR - PFS

1.1.3 Exploratory Objectives

Exploratory objectives	Endpoints
To evaluate patient-reported symptoms and health-related quality of life following treatment with acalabrutinib monotherapy	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)

To characterize the pharmacokinetics of acalabrutinib and its metabolite (ACP-5862)	Summarized plasma concentrations of acalabrutinib and ACP-5862 at specified time points Pharmacokinetic (PK) parameters by population analyses as appropriate
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1.2 Study Design

This global, Phase 3b, multicenter, open-label, single-arm study will evaluate the safety and efficacy of acalabrutinib 100 mg twice daily (bid) in approximately 540 participants with CLL.

Participants will be enrolled into 3 cohorts:

- Treatment-naïve (TN) cohort: participants who have had no prior treatment for CLL and who have either a score > 6 on the cumulative illness rating scale (See Appendix H of the Clinical Study Protocol) and/or have a creatinine clearance of 30 to 69 mL/min using the Cockcroft-Gault equation.
- Relapsed/refractory (R/R) cohort: participants who have previously had treatment for CLL and who have either relapsed or refractory CLL.
- Prior ibrutinib therapy cohort: participants who have received prior ibrutinib for CLL and who discontinued the medication for any reason prior to disease progression. The participant would need to be off ibrutinib for 30 days prior to receiving treatment in this study.

The general study design is summarized in [Figure 1](#). For this study, participants in the UK will be enrolled ONLY into the R/R cohort or the prior ibrutinib cohort. Participants in the US will be enrolled ONLY into the TN or R/R cohort.

Safety assessments will include AEs, SAEs, ECIs, AESIs, laboratory parameters (hematology, clinical chemistry, urinalysis, and others as clinically indicated), physical examinations and vital signs, and other tests deemed critical to the safety evaluation of the study intervention.

Assessment of response and progression will be conducted by the investigator in accordance with the iwCLL 2018 criteria ([Hallek, et al. 2018](#)). Overall response assessments will be based on evaluation of physical examinations, recording of symptoms, radiologic evaluations, and hematologic evaluations. Assessments will occur 1 year after the first study dose and per standard institutional practice and at investigator discretion, as clinically indicated.

This study will be monitored on an ongoing basis to ensure participants' safety by a DSMC. The first ISA occurred when approximately 100 participants had been treated in the study and followed up for approximately 12 cycles of study intervention or discontinued from the study for any reason. The second ISA was performed after a period of 12 months after the first ISA.

Additional safety reviews may be added based on recommendation by the DSMC, based on the first safety analysis review realized after full study enrollment.

Final analyses for this study will be performed after all participants complete treatment, ie, 48 cycles (or discontinue before) including 30 days of SFU. In events where participants have completed 48 cycles before the final DCO, they will continue to receive the study medication, if they benefit from it, until the final DCO.

Participants will remain on study intervention until completion of 48 cycles (28 days per cycle) or until study intervention discontinuation due to, for example, disease progression or toxicity, withdrawal of consent, loss to follow up, death, or study termination by the sponsor, whichever occurs first. If a participant continues to derive benefit from treatment at the end of 48 cycles prior to the final DCO, they will continue to be provided with study intervention and will be followed in the Disease Follow-up period q24w until study intervention discontinuation due to, for example, disease progression or toxicity, withdrawal of consent, loss to follow-up, death, or study termination by the sponsor, whichever occurs first. Alternatively, at the end of 48 cycles, a participant can decide to switch to commercial off-study acalabrutinib, if available and permitted by local regulations.

Post final DCO, 2 options will be considered: participants may be transitioned to another study or may shift to a commercial supply of acalabrutinib/off-study acalabrutinib as permitted by local regulations. Participants who switch to off study acalabrutinib will be considered as having completed the study and therefore will not have any additional study assessments, including the SFU visit and the Disease Follow-up period.

The duration of the study will be approximately 72 months from the first participant enrolled. This duration includes an estimated 24 month recruitment time and an assumed 48 cycles of study intervention (28 days per cycle); additional study time will be accrued during the Disease Follow up period for those participants remaining on study intervention after completion of 48 cycles prior to the final DCO (the amount of time will vary by participant).

At database lock, all ongoing participants, who have not transitioned to another study or to a commercial supply of acalabrutinib/off-study acalabrutinib, will be discontinued from the study and study intervention.

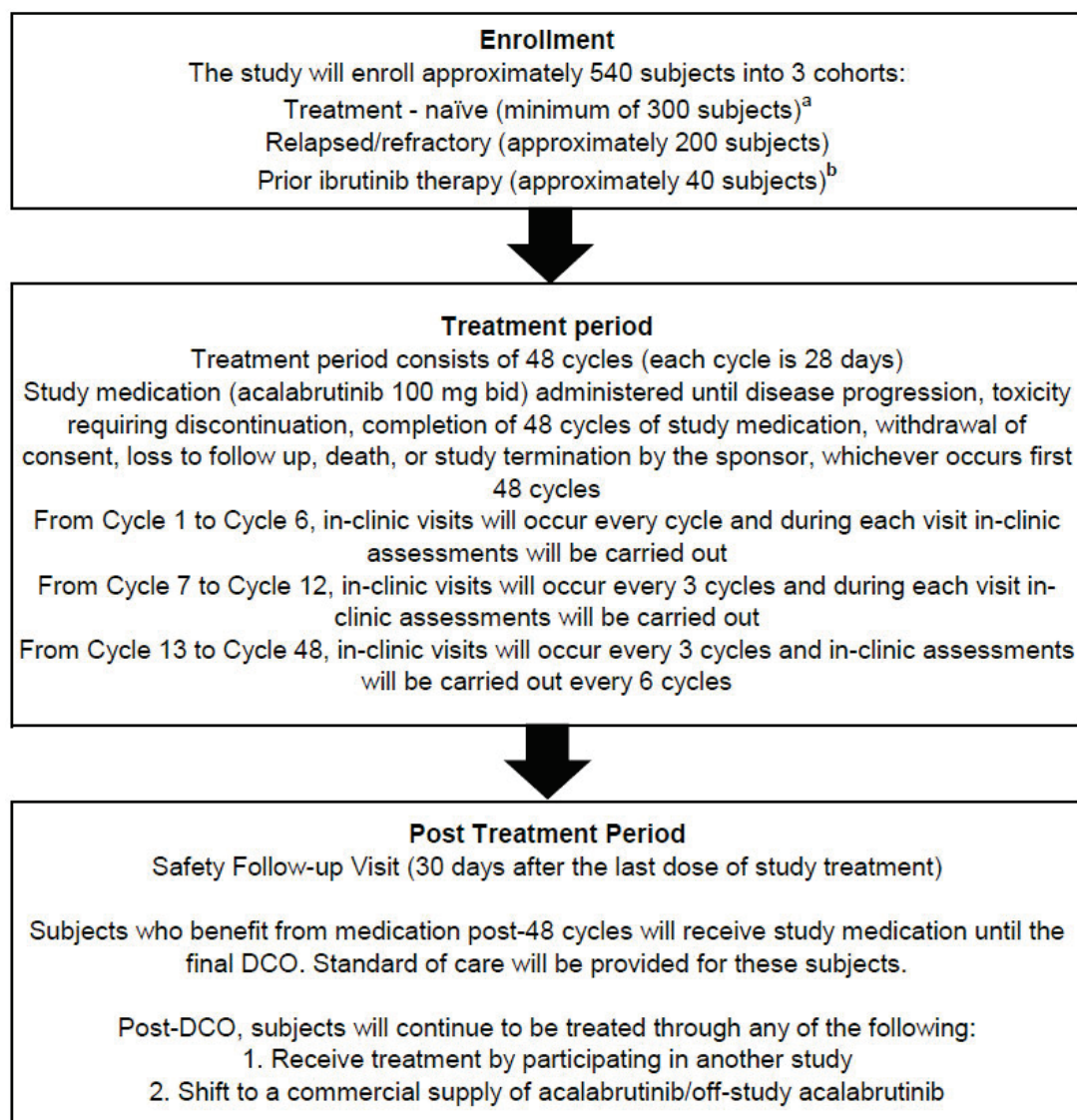
All participants will have a SFU visit no less than 30 days after the last dose of study intervention. A participant who experiences disease progression while on study intervention will need to complete the SFU visit just before shifting to new medication, or no less than 30 days, whichever occurs first.

Participants who switch to off-study acalabrutinib will be considered as having completed the study and therefore will not have any additional study assessments, including the SFU visit,

Disease Follow-up period, safety data assessment, collection, and reporting. They will follow the standard of care in that country.

Study procedures and their timing are summarized in the Schedule of Assessments (SoA) ([Appendix 1](#)). [Figure 2](#) presents the options for participants who complete the study.

Figure 1 Study Design



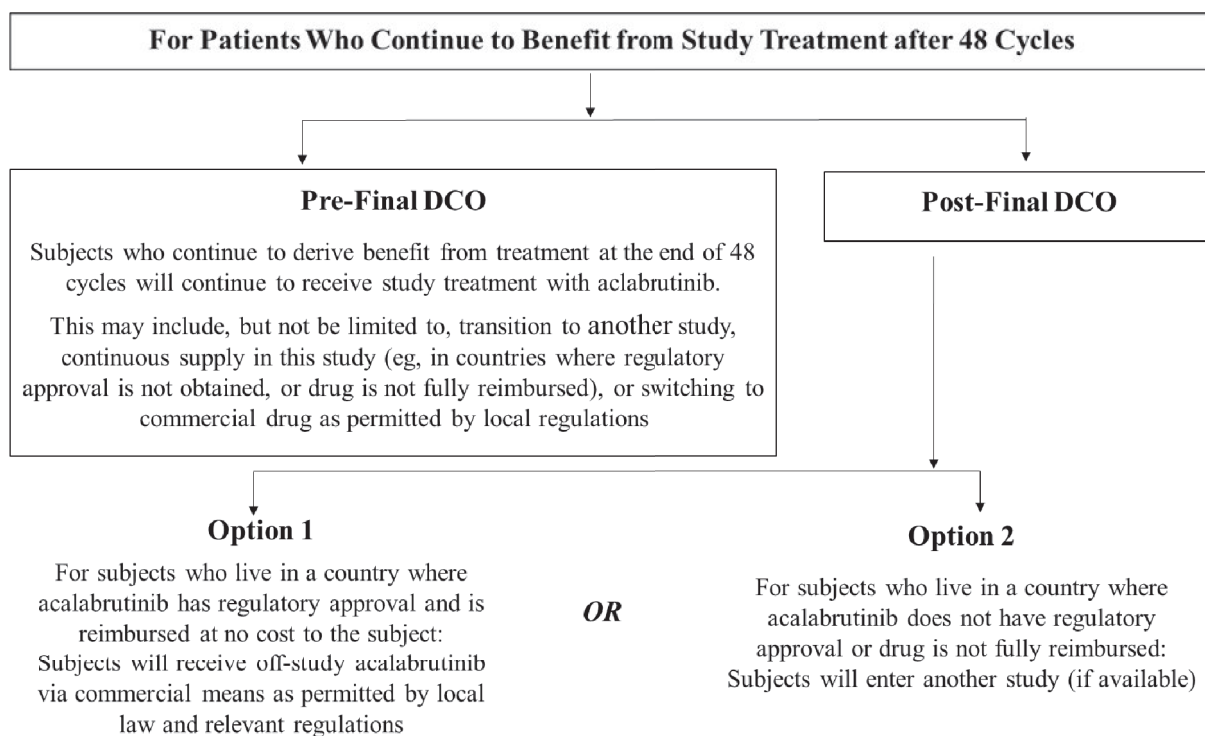
Note: If a participant continues to derive benefit from treatment at the end of 48 cycles prior to the final DCO, they will continue to be provided with study intervention. Post final DCO, 2 options will be considered: participants may be transitioned to another study or may shift to a commercial supply of acalabrutinib/off-study acalabrutinib as permitted by local regulation. Participants who switch to off-study acalabrutinib will be considered as having completed the study and therefore will not have any additional study assessments, including the Safety Follow-up visit and the Disease Follow-up period.

b) Participants in the United Kingdom will not be enrolled into the treatment-naïve cohort of this study. For this study, participants in the United Kingdom will be enrolled ONLY into the relapsed/refractory cohort or the prior ibrutinib cohort.

c) Participants in the United States will not be enrolled into the prior ibrutinib cohort of this study. For this study, participants in the United States will be enrolled ONLY into the treatment-naïve and relapsed/refractory cohort.

bid = twice daily; DCO = data cutoff.

Figure 2 Post-study Options



Note: See the SoA ([Appendix 1. Schedule of Assessments](#)) for the list of assessments that are required during the Disease Follow-up period.

Note: Serum pregnancy testing for WOCBP will be done at study site at screening. Serum or urine pregnancy testing should be done at each cycle, during the Disease Follow-up period every 4 weeks, at the SFU visit, and at any point when it is clinically indicated. Continuous contraception (as per protocol) is required until 2 days after last dose of acalabrutinib. If the pregnancy test does not correspond with a clinic visit, an option for pregnancy testing between cycle visits can be an at-home urine pregnancy test followed by a phone call from site staff to confirm the results. Alternatively, a pregnancy test (serum or urine) can be done in the clinic. Follow-up phone calls will be made to the female participant to confirm the results of the at-home urine pregnancy assessments. DCO = data cutoff; iwCLL = International Workshop on Chronic Lymphocytic Leukemia; q24w = every 24 weeks; SFU = Safety Follow-up; SoA = schedule of assessments.

1.3 Number of Participants

The study will enroll approximately 540 participants. Participants will be enrolled into 3 cohorts: TN, R/R, and prior ibrutinib therapy. Of the 540 participants to be enrolled, a minimum of 300 participants will be included in the TN cohort, approximately 200 participants in the R/R cohort and approximately up to 40 participants in the prior ibrutinib therapy cohort.

The sample size of 300 for the TN cohort and 200 for the R/R cohort was based on Study ACE-CL-001 (see [Table 1](#)), a dose-escalation study in participants with CLL/small lymphocytic lymphoma to determine a maximum tolerated dose.

Table 1 Participant Incidences of the Safety Endpoints in Participants with CLL Treated with Acalabrutinib (Study ACE-CL-001)

AE Category	Treatment-naïve Participants (n=99)	Relapsed/Refractory Participants (n=134)	All Participants (n=301)
SAE	26.3%	34.3%	34.2%
Grade ≥ 3 AE	38%	50.7%	48.2%
Major hemorrhage	1%	2.2%	2.0%
Atrial fibrillation	2%	3%	3.3%
Infection	57.6%	71.6%	64.8%
Hypertension	12.1%	12.7%	11.6%
AE leading to acalabrutinib discontinuation	3%	8.2%	6.6%

Note: The total (N=301) includes additional participants other than those in the treatment-naïve and relapsed/refractory cohorts.

AE=adverse event; CLL=chronic lymphocytic leukemia; SAE=serious adverse event.

The AE with the lowest incidence among R/R participants observed was 2.2%; there is 98.8% probability of observing ≥ 1 of a particular event in a sample of 200 participants if the true incidence of the event were 2.2%. The AE with the lowest incidence among TN participants observed was 1%; there is 95.1% probability of observing ≥ 1 of a particular event in a sample of 300 participants if the true incidence of the event were 1%. Given the proposed sample size of the R/R and TN subpopulations, [Table 2](#) provides an indication of the level of precision (exact Clopper-Pearson 95% CI) for an AE with varying observed incidence. The prior BTKi therapy cohort will serve as exploratory analysis cohort which is not considered in the sample size calculation and will account for up to 40 additional participants.

Table 2 Level of Precision (Exact 95% Confidence Interval) for Adverse Events with Varying Observed Incidence

	Precision (95% Confidence Interval) Estimate of Participant Incidence							
	0%	1%	3%	5%	10%	30%	50%	70%
100	0.0%, 3.6%	0.0%, 5.5%	0.6%, 8.5%	1.6%, 11.3%	4.9%, 17.6%	21.2%, 40.0%	39.8%, 60.2%	60.0%, 78.8%
200	0.0%, 1.8%	0.1%, 3.6%	1.1%, 6.4%	2.4%, 9.0%	6.2%, 15.0%	23.7%, 36.9%	42.9%, 57.1%	63.1%, 76.3%
300	0.0%, 1.2%	0.2%, 2.9%	1.4%, 5.6%	2.8%, 8.1%	6.9%, 14.0%	24.9%, 35.5%	44.2%, 55.8%	64.5%, 75.1%
500	0.0%, 0.7%	0.3%, 2.3%	1.7%, 4.9%	3.3%, 7.9%	7.5%, 13.0%	26.0%, 34.2%	45.5%, 54.5%	65.8%, 74.0%

The statistical analyses will be performed at a minimum of three time points:

- when approximately 100 participants have been treated for 12 cycles (first interim safety analysis).
- after a period of 12 months after the first interim analysis (second interim safety analysis).
- at the end of the study (final analysis).

2 ANALYSIS SETS

2.1 Definition of Analysis Sets

With the exception of some summaries and individual participant listings, which will be produced using all enrolled participants, the following 2 analysis sets are defined and will be used for listings, summaries and analyses:

- Safety Analysis Set (SAF): participants who receive ≥ 1 dose (partial or in full) of study intervention. The safety analyses, disposition, and baseline characteristics will be conducted on the SAF. In this safety study, the standard full analysis set will be same as SAF, therefore, the SAF will be used for analysis of efficacy endpoints as well.
- Pharmacokinetic Analysis Set (PKAS): participants in the SAF who have ≥ 1 evaluable post treatment PK value. The PKAS will be used for all summaries of PK data.

2.2 Protocol Deviations

According to ICH E3 guidelines version dated 1995 (ICH 1995),

“Protocol deviations consist of any change, divergence or departure from the study design or procedures defined in the protocol. Important protocol deviations (IPDs) are a subset of protocol deviations that may significantly affect the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient’s rights, safety or well-being.”

For this study, IPDs will include, but are not limited to, the following 4 general categories and will be summarized in the CSR:

- Deviation 1: Participants who received treatment and who deviated from the following key entry criteria in CSP:
 - Inclusion Criterion 1: Men and women ≥ 18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place)
 - Inclusion Criterion 2: Diagnosis of CLL that meets all published diagnostic criteria ([Hallek, et al. 2018](#)) as stated below:
 - a. Monoclonal B-cells (either kappa or lambda light chain restricted) that are clonally co-expressing ≥ 1 B-cell marker (CD19, CD20, and CD23) and CD5 during screening.
 - b. Prolymphocytes may comprise $< 55\%$ of blood lymphocytes during screening.
 - c. Presence of $\geq 5 \times 10^9$ B lymphocytes/L (5000/ μ L) in the peripheral blood (at any point since the initial diagnosis).
 - Inclusion Criterion 3: Active disease per at least 1 of the following iwCLL 2018 criteria
 - a. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia (hemoglobin < 10 g/dL) and/or thrombocytopenia (platelets $< 100,000/\mu$ L)
 - b. Massive (i.e., ≥ 6 cm below the left costal margin), progressive, or symptomatic splenomegaly
 - c. Massive nodes (i.e., ≥ 10 cm in the longest diameter), progressive, or symptomatic lymphadenopathy
 - d. Progressive lymphocytosis with an increase of $>50\%$ over a 2-month period or a lymphocyte doubling time (LDT) of < 6 months. LDT may be obtained by linear regression extrapolation of absolute lymphocyte count obtained at intervals of 2 weeks over an observation period of 2 to 3 months. In participants with initial blood lymphocyte counts of $< 30 \times 10^9/\text{L}$ (30,000/ μ L), LDT should not be used as a single parameter to define indication for treatment. In addition, factors contributing to

lymphocytosis or lymphadenopathy other than CLL (e.g., infections) should be excluded.

- e. Autoimmune anemia and/or thrombocytopenia that is poorly responsive to standard therapy.
 - f. B-symptoms documented in the participant's chart with supportive objective measures, as appropriate, defined as ≥ 1 of the following disease-related symptoms or signs:
 - Unintentional weight loss $\geq 10\%$ within the previous 6 months before screening
 - Significant fatigue (Eastern Cooperative Oncology Group [ECOG] performance status ≥ 2 ; inability to work or perform usual activities)
 - Fevers higher than 100.5°F or 38.0°C for ≥ 2 weeks before screening without evidence of infection
 - Night sweats for ≥ 1 month before screening without evidence of infection
- Inclusion Criterion 4: Must meet 1 of the following criteria:
 - a. Have received no prior therapy for treatment of CLL and meets one of the following criteria (for this study, participants in the UK will be enrolled ONLY in the R/R or the prior ibrutinib cohort):
 - A score of > 6 on the CIRS
 - Creatinine clearance of 30 to 69 mL/min using the Cockcroft-Gault equation
 - b. Have previously received therapy for CLL and have either refractory or relapsed CLL.
 - c. Have received prior ibrutinib therapy (ie, defined as a participant who discontinued ibrutinib for any reason prior to disease progression) for CLL (participants in the US will not be enrolled into the prior ibrutinib therapy cohort)
 - Intolerance of ibrutinib, defined as:
 - The participant discontinued ibrutinib therapy due to Grade 3 or 4 AEs that persisted in spite of optimal supportive care measures or
 - Participant had Grade 2 AEs related to ibrutinib therapy, in spite of optimal supportive care measures that persisted for ≥ 2 weeks or that recurred ≥ 2 times whether dose was reduced or discontinued.
 - Inclusion Criterion 5: ECOG performance status of ≤ 2

- Inclusion Criterion 6: Female participants of childbearing potential (ie, not surgically sterile or post-menopausal) who are sexually active with a non-sterilized male partner must use ≥ 1 highly effective method of contraception from the time of screening and must agree to continue using such precautions for 2 days after the last dose of study treatment. Contraception measures and restrictions on sperm donation are not required for male participants.
- Inclusion Criterion 7: Fluorescence in situ hybridization (FISH) for which the next-generation sequencing (NGS) method is preferred) within 60 days during screening up to before the first dose reflecting the presence or absence of del(17p), 13q del, 11q del, and trisomy of chromosome 12 along with the percentage of cells with the deletion, along with TP53 sequencing. Participants must also have molecular analysis to detect IGHV mutation status (NGS is the preferred method) at screening if not done at any time point before that since diagnosis. The results of these tests (FISH, TP53, and IGHV) are not required to start dosing the participants.
- Inclusion Criterion 8: Each participant (or legally authorized representative if allowed per local regulations) must be willing and able to adhere to the study visit schedule, understand and comply with other protocol requirements, and provide written informed consent and authorization to use protected health information.
- Exclusion Criterion 1: Participants who have had disease progression while on a BTKi for any malignant or non-malignant condition
- Exclusion Criterion 2: Prior malignancy (other than CLL), except for adequately treated basal cell or squamous cell skin cancer, in situ cancer, early-stage prostate cancer, or other cancer from which the participant has been disease-free for ≥ 2 years
- Exclusion Criterion 3: History of confirmed progressive multifocal leukoencephalopathy
- Exclusion Criterion 4 Significant cardiovascular disease such as symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months before screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or corrected QT interval using Fridericia's formula (QTcF) > 480 msec at screening. Note: Participants with rate-controlled, asymptomatic atrial fibrillation are allowed to enroll in the study (For prior ibrutinib therapy cohort only).
- Exclusion Criterion 5: Malabsorption syndrome, disease significantly affecting gastrointestinal function, resection of the stomach, extensive small bowel resection that is likely to affect absorption, symptomatic inflammatory bowel

disease, partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass

- Exclusion Criterion 6: Evidence of active Richter's transformation. If Richter's transformation is suspected (i.e., lactate dehydrogenase [LDH] increased, asymmetric fast lymph node growth or clinical suspicion), it should be ruled out with positron emission tomography-computed tomography (PET-CT) and/or biopsy according to guidelines
- Exclusion Criterion 7: Central nervous system involvement by CLL
- Exclusion Criterion 8: Known history of human immunodeficiency virus, serologic status reflecting active hepatitis B virus or hepatitis C virus infection, any uncontrolled active systemic infection along with participants who are on ongoing anti-infective treatment and participants who have received vaccination with a live attenuated vaccine within 4 weeks before the first dose of study treatment
 - a. Participants who are hepatitis B core antibody (anti-HBc) positive and who are hepatitis B surface antibody (anti-HBs) negative will need to have a negative hepatitis B virus PCR result before enrollment. Those who are hepatitis B surface antigen (HBsAg) positive or hepatitis B virus PCR positive will be excluded.
 - b. Participants who are hepatitis C virus antibody positive will need to have a negative hepatitis C virus PCR result before enrollment. Those who are hepatitis C virus PCR positive will be excluded.
- Exclusion Criterion 9: Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura defined as declining hemoglobin or platelet count secondary to autoimmune destruction within the screening period or requirement for high doses of steroids (> 20 mg daily of prednisone or equivalent for longer than 2 weeks).
- Exclusion Criterion 10: History of stroke or intracranial hemorrhage within 6 months before the first dose of study treatment.
- Exclusion Criterion 11: History of bleeding diathesis (eg, hemophilia or von Willebrand disease).
- Exclusion Criterion 12: Presence of a GI ulcer diagnosed by endoscopy within 3 months before screening.
- Exclusion Criterion 13: Major surgical procedure within 4 weeks before first dose of study treatment. Note: participants who have had major surgery must have recovered adequately from any toxicity and/or complications from the intervention before the first dose of study treatment.

- Exclusion Criterion 14: Requires treatment with proton-pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). Participants receiving proton-pump inhibitors who switch to H2-receptor antagonists or antacids are eligible for enrollment in this study
 - Exclusion Criterion 15: All participants requiring or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon) within 7 days before first dose of study treatment. Based on the known metabolic/transport pathways involved in the disposition of acalabrutinib and the commonly known novel oral anticoagulants (eg, apixaban, rivaroxaban, and edoxaban), no clinically relevant interaction is expected following coadministration of these agents.
 - Exclusion Criterion 16: Absolute neutrophil count (ANC) $< 0.50 \times 10^9/L$ or platelet count $< 30 \times 10^9/L$, unless proven due to CLL and raised above the limits by granulocyte colony-stimulating factor (G-CSF) therapy and/or pooled platelet transfusion.
 - Exclusion Criterion 17: Total bilirubin $> 3.0 \times$ upper limit of normal (ULN); or aspartate aminotransferase or alanine aminotransferase $> 3.0 \times$ ULN. Exception will be for Gilbert syndrome; if an investigator feels that a participant's total bilirubin is elevated secondary to Gilbert's, the participant must have a documented unconjugated bilirubin being $> 80\%$ of the total bilirubin number. The investigator must also document that hemolysis has been ruled out along with (near)-normal lactate dehydrogenase and haptoglobin
 - Exclusion Criterion 18: Estimated creatinine clearance of < 30 mL/min, calculated using the formula of Cockcroft and Gault or by direct assessment (i.e., creatinine clearance or ethylene diamine tetra-acetic acid (EDTA) clearance measurement)
 - Exclusion Criterion 19: Breastfeeding or pregnant
 - Exclusion Criterion 20: Received any chemotherapy, external beam radiation, investigational drug, or any other anti-CLL therapy within 30 days before first dose of study treatment
 - Exclusion Criterion 21: Concurrent participation in another therapeutic clinical study.
 - Exclusion Criterion 22: History of or ongoing interstitial lung disease.
 - Exclusion Criterion 23: Requiring long-term (> 1 week) treatment with a strong cytochrome CYP3A inhibitor/inducer. In addition, the use of strong or moderate CYP3A inhibitors or inducers within 7 days of the first dose of study drug is prohibited.
- Deviation 2: The participant met discontinuation criteria but did not discontinue

acalabrutinib (eg, participant withdrew consent, participant became pregnant).

- Deviation 3: The participant received for a long-term period (> 1 week) a prohibited concomitant medication or therapy, as detailed in Appendix F of the Clinical Study Protocol, or any other concomitant medication or therapy which, upon physician review of all medications prior to the final DCO, is considered to have a potential effect on study outcomes.
- Deviation 4: Missed visits, assessments, or treatments with significant effect on completeness, accuracy, or reliability of the participant's data, rights, safety, or well-being related to 2020 COVID-19 global pandemic. IPDs will be identified by the study team during the IPD reviews throughout the study. The final classification of IPDs will be made prior to database lock. Decisions made will be documented and approved by AstraZeneca prior to analysis.

3 PRIMARY AND SECONDARY VARIABLES

3.1 Safety Variables

3.1.1 Adverse Events

The primary safety endpoints are treatment-emergent AEs with Grade ≥ 3 , SAEs, AESIs, AEs that lead to discontinuation of treatment, and ECIs.

AEs (from first dose) and SAEs (from screening, if related to a study procedure) will be collected throughout the treatment period defined as period from the start of enrollment until study treatment discontinuation. During the follow-up period, all AEs, SAEs, ECIs, and AESIs are required to be collected. AEs will be graded by the investigator according the National Cancer Institute CTCAE (version 5.0). Each AE verbatim term will be coded to a system organ class (SOC) and a preferred term using the Medical Dictionary for Regulatory Activities (MedDRA).

Treatment-emergent AEs (TEAEs) are defined as AEs that start after first dose of acalabrutinib or which start prior to the first dose of acalabrutinib but worsen following the first dose of acalabrutinib, and where the start date of worsening is also no later than 30 days after the date of the last dose of acalabrutinib or the first date starting new anticancer therapy, whichever is earlier. Any AEs with onset date after the start of subsequent anticancer therapy will not be considered as a TEAE.

Subsequent anticancer therapies will be determined using the ATC codes in the concomitant medication data. Subsequent anticancer therapies are defined as use any of the following concomitant medications after the start date of acalabrutinib treatment: Ibrutinib,

Zanubrutinib, Pirtobrutinib, Venetoclax, Idelalisib, Duvelisib, Rituximab, Obinutuzumab, Ofatumumab.

Only TEAEs will be included in the AE summary tables. Any events that occur after a participant has received further therapy for cancer will be flagged in the data listings. Any AE occurring before acalabrutinib (i.e. before the administration of the first dose) will be included in the AE listings, but will not be included in the summary tables (unless otherwise stated). These will be referred to as ‘pre-treatment’. However, any AE occurring before the administration of the first dose of acalabrutinib that increases in severity after the first dose will be regarded as treatment emergent.

For participant level summaries, if more than one AE is coded to the same preferred term for the same participant, the participant will be counted only once in summary tables using the most severe grading. For AE summaries by relatedness to study drug and AE severity, the most severe grading on causal relationship to acalabrutinib will be used.

3.1.1.1 Events of Clinical Interest

An ECI may be serious or non-serious. Acalabrutinib ECIs include the categories: cardiac disorder events, hepatotoxicity, hypertension, infections, interstitial lung disease/pneumonitis, hemorrhage (major hemorrhage), cytopenias (anemia, leukopenia, thrombocytopenia), second primary malignancies, and tumor lysis syndrome. ECI categories are listed in [Appendix 2](#) and may be modified depending on the emerging safety profile of acalabrutinib.

3.1.1.2 Adverse Events of Special Interest

The following events are considered AESIs: Ventricular arrhythmias (eg, Torsade de pointes, ventricular extrasystoles, ventricular tachycardia, ventricular arrhythmia, ventricular fibrillation, ventricular flutter, and ventricular tachyarrhythmia). The list of MedDRA preferred terms for these AESIs are listed in the [Appendix 3](#).

3.1.1.3 Physical Examination

A physical examination will be performed at Screening and during the study. Abnormal physical examination findings at Screening be reported as medical history. Abnormal physical examination findings that are clinically significant and occur after the first dose of study treatment will be reported as an AE.

3.1.2 Laboratory Variables

Laboratory data will be collected throughout the study, from screening to the follow-up visits as per the study plan described in the CSP. Hematology (including CD3+, CD19+, CD4+, CD8+, CD16+/56+), clinical chemistry, and others as clinically indicated will be collected as

described in Section 5.2.2 of the CSP. For the definition of baseline and how to handle missing data, the criteria described in Section 3.4 will be used. Laboratory values will be summarized using standard units (SI units).

- Change from baseline in hematology (including CD3+, CD19+, CD4+, CD8+, CD16+/56+) and clinical chemistry variables will be calculated for each visit throughout the treatment period after last dose of acalabrutinib. Common toxicity criteria (CTC) grades will be defined at each visit according to the CTC grade criteria using local ranges as required.

The maximum (or minimum) on-treatment value (depending on the direction of an adverse effect) will be defined for each laboratory parameter as the maximum (or minimum) post-dose value at any time.

Local reference ranges will be used for the primary interpretation of laboratory data at the local laboratory; local reference ranges will also be used throughout for reporting purposes. The denominator used in laboratory summaries of CTC grades will only include evaluable participants, in other words those who had sufficient data to have the possibility of an abnormality.

For example:

- If a CTC criterion involves a change from baseline, evaluable participants would have both a baseline and at least one post-dose value recorded.

If a CTC criterion does not consider changes from baseline, to be evaluable the participant needs only to have one post-dose value recorded.

3.1.3 Treatment Exposure and Compliance

Acalabrutinib is taken twice daily. The elimination half-life of acalabrutinib in humans is generally 1-3 hours, and for the metabolite ACP-5862 it is approximately 7 hours. Accounting for an elimination exposure of 2 days (i.e. 4.5 half-lives of the metabolite), the total duration of exposure time (months) of acalabrutinib will be calculated as follows:

- Total (or intended) exposure (months) = [minimum of (last dose date where dose > 0mg + 2 days, date of death, DCO date) - first dose date + 1] / 30.4375

Actual duration of exposure (months) of acalabrutinib will be calculated as follows:

- Actual duration of exposure = total (or intended) exposure – total duration of dose interruptions in months (where dose = 0 mg), where total exposure will be calculated as

above and a dose interruption is defined as any length of time where the participant has not taken any of the planned dose. The actual exposure calculation makes no adjustment for any dose reductions that may have occurred.

Relative dose intensity (RDI) is the percentage of the actual cumulative dose delivered (d) relative to the intended cumulative dose (D) through to treatment discontinuation. RDI will be defined as follows:

$$RDI (\%) = 100 \times \frac{d}{D}$$

Actual cumulative dose is a sum of all actual doses (including potentially reduced doses such as 100 mg daily) taken through the treatment duration and will be presented in grams. For scheduled drug administration visits that are skipped the actual dose will be 0.

Intended cumulative dose is a sum of all planned doses that had to be taken during the treatment duration in grams. The total daily intended dose for this study is 200 mg. Average daily dose (mg) for acalabrutinib is total cumulative dose received (mg) divided by duration of exposure in days.

3.2 Efficacy Variables

3.2.1 Overall Response

Overall response will be defined as a participant's best OR to the treatment. A participant will be considered a responder if s(he) achieves CR, CRi, or PR, according to the iwCLL 2018 criteria ([Hallek, et al. 2018](#)), as assessed by the investigator. The ORR is defined as the proportion of participants who are considered responders. The corresponding 95% 2-sided CIs will be derived for ORR. Data obtained up until progression, or last evaluable overall response assessment in the absence of progression, will be included in the assessment of OR. Participants who do not meet the criteria for OR will be considered non-responders.

3.2.2 Duration of Response

DOR analysis will include only participants who were responders (i.e. with an OR of CR, CRi or PR). DOR is defined as the time from the first OR of CR, CRi, or PR to the time of documented disease progression or death due to any cause, whichever occurs first. Participants who are progression-free and alive at the time of data cut-off or have unknown status will have DOR right-censored at the time of their last disease assessment (defined as, the last visit where both haematology and physical exam present/performed) on or before data cut-off.

3.2.3 Progression Free Survival

PFS is defined as the interval from the start of study treatment to the earlier of the first documentation of disease progression or death from any cause (i.e. date of PFS event or censoring – date of first dose of acalabrutinib + 1). Participants who are progression-free (participants who doesn't meet iwCLL criteria for progression) and alive at the time of data cut-off or have unknown status will have PFS right-censored at the time of their last disease assessment (that is, the last visit where both haematology and physical exam present/performed) on or before data cut-off. Participants who withdrew without a disease progression event and do not have any post-baseline disease assessment (that is, haematology and physical exams) will be censored at the date of first study treatment.

3.2.4 Patient-reported Health-related Quality of Life and Symptoms

PROs will be assessed using the EORTC QLQ-C30 and PRO CTCAE. All items/questionnaires will be scored according to published scoring guidelines. All PRO analyses will be based on the SAF and reported separately for each of the 3 cohorts. All PROs are exploratory outcomes in this study.

3.2.4.1 EORTC-QLQ-C30

The EORTC QLQ-C30 consists of 30 items and measures cancer patients' symptoms, functioning, and HRQoL ([Aronson, et al. 1993](#)) for all cancer types. The items are either used individually to create an item score or are combined to make a scale score:

- Five multi-item functional scale scores: Physical Functioning (Questions 1 to 5), Role Functioning (Questions 6 and 7), Emotional Functioning (Questions 21 to 24), Cognitive Functioning (Questions 20 and 25), and Social Functioning (Questions 26 and 27)
- Three multi-item symptom scale scores: Fatigue (Questions 10, 12 and 18), Pain (Questions 9 and 19), Nausea and Vomiting (Questions 14 and 15)
- Five single-item symptom scores: Dyspnea (Question 8), Loss of Appetite (Question 13), Insomnia (Question 11), Constipation (Question 16), and Diarrhea (Question 17);
- One single-item score for Financial Impact of the Disease (Question 28)
- One two-question global HRQoL scale score (Questions 29 and 30)

For Questions 1 to 28, responses are on a 4-point scale with the format: 1 = “not at all”, 2 = “a little”, 3 = “quite a bit”, and 4 = “very much”.

For Questions 29 and 30, the response is on a 7-point scale ranging from 1 (“very poor”) to 7 (“excellent”).

Single-item scores and multi-item scales all range from 0 to 100. Higher scores on the global HRQoL scale and the five functional scales indicate better health status/function, but higher scores on symptom scores/scales represent greater symptom severity/burden.

Calculation of final scores is as follows:

- If 50% or more of the items in a scale are non-missing (ie, 1 for single-item scores, at least 1 for 2-item scores, and at least 2 for 3-item scores), calculate the raw score (RS) as the average of the non-missing items that contribute to the scale, otherwise the RS is missing.
- If a RS is missing, the corresponding final score is missing, otherwise the RS is transformed into the final score as follows:
 - Functional Scales: $\text{Score} = 100 * (4 - \text{RS}) / 3$
 - Any symptom score: $\text{Score} = 100 * (\text{RS} - 1) / 3$
 - HRQoL Scale: $\text{Score} = 100 * (\text{RS} - 1) / 6$

Definition of compliance and evaluability rates

Compliance rates for the EORTC QLQ-C30 will be calculated:

$$\text{Compliance rate} = \frac{\text{number of evaluable forms}}{\text{number of expected forms}} \times 100$$

Evaluability rates for the EORTC QLQ-C30 will also be calculated:

$$\text{Evaluability rate} = \frac{\text{number of evaluable forms}}{\text{number of received forms}} \times 100$$

Where an expected, evaluable and received questionnaire is defined as follows:

- Expected questionnaire = a questionnaire that is expected to be completed at a scheduled assessment time, i.e. a questionnaire from a participant who has not withdrawn from the study at the scheduled assessment time but excluding participants in countries with no available translation (exclusion across all visits) and participants who could not complete questionnaire due to no available internet or lack of devices (visit-specific exclusion).
- Evaluable questionnaire = a questionnaire with a completion date and at least one subscale that is non-missing.
- Received questionnaire = a questionnaire that has been received and has a completion date and at least one individual item completed.

Definition of clinically meaningful changes

Changes in score compared to baseline will be evaluated. A minimum clinically relevant change is defined as a change in the score from baseline of ≥ 10 for scales/items from the QLQ-C30 (Osoba, et al. 1998).

For example, a clinically relevant improvement in fatigue (as assessed by QLQ-C30) is defined as a decrease in the score from baseline of ≥ 10 . At each post-baseline assessment, change in symptoms/functioning from baseline will be categorized as improved, stable, or worsening as shown in Table 3. Participants with no baseline data will be excluded from analyses.

Table 3 Visit response for symptoms and HRQoL

Score	Change from Baseline	Visit Response
QLQ-C30 symptom scales/items	$\geq + 10$	Worsened
	$\leq - 10$	Improved
	Otherwise	Stable
QLQ-C30 functional scales and global health status/QoL	$\geq + 10$	Improved
	$\leq - 10$	Worsened
	Otherwise	Stable

3.2.4.2 PRO-CTCAE

The PRO version of the CTCAE is an item-bank of symptoms experienced by patients while undergoing treatment of their cancer. This was based on findings from multiple studies demonstrating that physicians and nurses underestimate symptom onset, frequency, and severity in comparison with patient ratings (Sprangers and Aaronson 1992; Litwin, et al. 1998; Aaronson, et al. 1993; Basch, et al. 2009).

For several symptoms, like fatigue and pain, additional questions are asked about symptom frequency, severity, and interference with usual activities. For other symptoms like rash, additional questions focus on the presence on the body. For this study, 13 items are considered relevant and will be assessed: headache, diarrhea, fatigue, nausea, vomiting, abdominal pain, rash, muscle pain, nose bleed, heart palpitations, bruising, joint pain, and constipation. The valid responses are:

- Frequency responses: Never / Rarely / Occasionally / Frequently / Almost constantly
- Severity responses: None / Mild / Moderate / Severe / Very severe
- Interference responses: Not at all / A little bit / Somewhat / Quite a bit / Very much

3.3 Baseline Variables

3.3.1 Age

If age is missing but date of birth is present, age will be calculated as follows (without rounding):

$$\text{Age (years)} = (\text{date of informed consent} - \text{date of birth}) / 365.25$$

This will be determined from the date of birth (birth date in the Demographics eCRF page) and Informed Consent Form (ICF) date. For some countries, only partial birth date is collected on the eCRF. In those cases, if the day of birth is missing, the first day of the month will be imputed and if day and month are missing January 1st will be imputed.

3.3.2 Time from Original Diagnosis

Time from original diagnosis (months) will be calculated as follows:

$$\text{Time from original diagnosis (months)} = (\text{Cycle 1 Day 1} - \text{original diagnosis date} + 1) / 30.4375$$

If the original diagnosis day is missing, the first day of the month will be imputed, and if day and month are missing January 1st will be imputed.

3.3.3 Prior and Concomitant Medications and Procedures

The World Health Organization Drug Dictionary (WHODrug) will be used for concomitant and prior medications coding. Concomitant procedures will be coded using the latest version of MedDRA.

Concomitant medications and procedures will be recorded from screening at every visit.

Any medications taken by the participant prior to or during screening with a stop date prior to the first dose of acalabrutinib will be considered prior medication.

Any medication taken by the participant at any time after the date of the first dose (including the date of the first dose) of acalabrutinib up to 30 days after last dose will be considered concomitant medication. Any medication that started prior to the first dose of acalabrutinib and ended after the first dose or is ongoing will be considered as both prior and concomitant medication.

For the purpose of inclusion in prior or concomitant medication summaries, incomplete medication start and stop dates will be imputed as detailed in Section [4.1.3](#).

3.3.4 Medical History

Medical history (past and current) and surgical history will be coded using the latest version of MedDRA.

4 ANALYSIS METHODS

4.1 General Principles

4.1.1 General Statistical Considerations

No hypothesis testing is planned for this single-arm study.

The below mentioned general principles will be followed throughout the study:

- Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each category.
- For continuous data the mean and median will be rounded to one additional decimal place compared to the original data. The standard deviation will be rounded to two additional decimal places compared to the original data. Minimum and maximum will be displayed with the same accuracy as the original data.
- For categorical data, percentages will be rounded to one decimal place.
- SAS[®] version 9.3 or higher will be used for all analyses.
- For time interval analyses in months, duration in months will be calculated as total duration in days / 30.4375.
- Exact CIs for proportions will be calculated using the Clopper-Pearson method.
- For percentiles based on the Kaplan-Meier method (eg, median PFS), CIs will be calculated using the default method available in the SAS LIFETEST procedure (ie, the Klein and Moeschberger extension of the Brookmeyer-Crowley method). For the 10th percentile based on the Kaplan-Meier method, CIs will be calculated using the default method available in the SAS QUANTLIFE procedure.
- For point-estimates based on the Kaplan-Meier method (eg, for PFS at 12 months), CIs will be calculated using the default method available in the SAS LIFETEST procedure (ie, using Greenwood's estimate of standard error and a log-log transformation).

4.1.2 Definition of Baseline

Baseline will be defined as the last non-missing measurement prior to dosing with acalabrutinib. Assessments on the day of the first dose where neither time nor a nominal pre-dose indicator are captured will be considered prior to the first dose if such procedures are

required by the CSP to be conducted before the first dose. Where safety data are summarized over time, study day will be calculated in relation to date of first dose of acalabrutinib.

The baseline value for the safety analysis will be defined as the value collected at the time closest to and before the start of study treatment. Incomplete AE start and stop dates will be imputed as detailed in Section 4.1.3

4.1.3 Handling of Missing Data

In general, other than for partial dates, missing safety data will not be imputed and will be treated as missing. However, in all data presentations (except listings), safety assessment values below the limit of quantification (BLQ) will be imputed as ‘lower limit of quantitation (LLQ)’, where LLQ will be replaced with the value for the lower limit of quantification. In listings, BLQ values will be reported as ‘< LLQ’. In addition, AEs that have missing relatedness will be assumed to be related to acalabrutinib.

The general imputation rule for a missing start or end date of a concomitant medication or AE, the start date of subsequent anticancer therapy, or the date of initial diagnosis is:

- If year is missing (or completely missing), do not impute.
- If year and month are present and day is missing, impute day as the 15th of the month.
- If (year is present and month and day are missing) or (year and day are present and month is missing), impute as June 30th.

In addition, for AEs, if for a partial start date, the AE start date could (when also considering the AE end date) potentially be on the first dose of acalabrutinib date, the AE start date will be imputed with the first dose of acalabrutinib date to assume a “worst case” scenario; e.g. AE from UNK-Jun-2017 to 23-Jul-2017 with the first dose of acalabrutinib date 21-Jun-2017, then the AE start date will be imputed to 21-Jun-2017.

If the imputed AE start date is after the AE end date, then the AE end date will be used.

If the imputed AE end date is before the AE start date, the AE start date will be used. If the imputed AE end date is on or after the death date, the date of death will be used.

For medications, a conservative approach will be followed and will be assumed to be concomitant unless the end date is before the first dose of acalabrutinib. If the start and end dates are both missing it is considered concomitant.

If imputed initial diagnosis is on or after date of first dose of acalabrutinib, the date of first dose – 1 will be used.

If imputed date of subsequent anticancer therapies is before the date of last dose of acalabrutinib, the date of last dose + 1 will be used.

4.1.4 COVID-19 Impact

Depending on the extent of any impact, summaries of data relating to impact of COVID-19 on study conduct (in particular missed visits, delayed or discontinued IP, and other protocol deviations) may be generated, by treatment group, including:

- Disposition (discontinued IP due to COVID-19 and withdrew study due to COVID-19).
- Deviations (overall deviations plus if due to COVID-19 and not due to COVID-19).
- Summary of COVID-19 disruption (visit impact, drug impacted).
- Listing for patients affected by the COVID-19 pandemic.

4.2 Demographic and Baseline Characteristics

4.2.1 Participant Disposition

Participant disposition, including screening failures, reason for screening failure, reason for permanent discontinuation from acalabrutinib or withdrawal from follow-up, and number of participants in each analysis population (SAF, PKAS) will be summarized and listed by cohort and overall. Participants that have discontinued treatment will be listed for the SAF.

A summary of COVID-19 study disruptions will be presented as well as a summary table of participants with confirmed/suspected COVID-19 infections. A listing will be generated to outline the participants affected by the COVID-19 pandemic.

Participant recruitment by region, country and investigative site will be tabulated by cohort and overall for all enrolled participants.

4.2.2 Protocol Deviation

All identified IPDs will be listed and summarized for the SAF.

The number and percentage of participants with any IPD will be summarized for each IPD category. Participants with more than one deviation in the same IPD category will be counted once for that IPD category. Any participants who have deviations in more than one IPD category will be counted once in the overall summary.

4.2.3 Demographics and other baseline characteristics

The following participant demographic and baseline characteristics will be summarized and listed for the SAF and PKAS and will be repeated for participants with confirmed/suspected COVID-19 infection for the SAF:

- Sex, race, ethnicity
- Age at screening, age group [< 50 ; $\geq 50 - < 65$; ≥ 65 years and additionally ≥ 75 years]
- Height (cm), Weight (kg), body mass index (BMI)

Smoking status and number of pack-years will be summarized for the SAF. Pack-years is a standardized measure used to quantify cumulative exposure to cigarette smoking. It is calculated as:

$$\text{Pack-years} = \text{Number of packs smoked per day} \times \text{Number of years smoked}$$

One pack is typically defined as 20 cigarettes. For example, someone who smoked 1 pack per day for 20 years has 20 pack-years.

4.2.4 Disease History

Disease characteristics at baseline, including ECOG Performance Status, Cumulative Illness Rating Scale (CIRS), FISH and karyotyping will be summarized in the SAF by cohort and overall.

Extent of disease upon entry to study, including evaluation method, Rai and Binet stage, radiological assessment, evidence of disease, site of local/metastatic disease and recurrence of earlier cancer will be summarized for all participants in the SAF by cohort and overall.

Previous cancer therapy will be summarized in the SAF by cohort and overall.

4.2.5 Medical History

Medical and surgical history and baseline physical examination findings will be summarized and listed for the SAF and repeated for participants with confirmed/suspected COVID-19 infection.

4.2.6 Prior Medications

Prior medications (with a start date prior to study treatment start date) will be coded using the latest version of WHODrug and will be listed only.

4.3 Analysis of Safety Data

All safety data will be summarized by cohort and overall based on the SAF.

4.3.1 Exposure and Compliance

Exposure (total and actual) to acalabrutinib will be summarized and listed for the SAF in terms of the duration of treatment in months (mean, median and range). Actual cumulative dose and average daily dose (mean, median and range), RDI, dose modifications, dose interruptions, dose delays will also be summarized. These outputs may be repeated for participants with confirmed/suspected COVID-19 infection.

4.3.2 Adverse Events

Only TEAEs (see Section 3.1.1) will be summarised. Any AE occurring before the first dose of acalabrutinib and AEs occurring more than 30 days after last dose will be listed only and not included in the summaries.

All AEs will be summarised descriptively for the SAF, in terms of number of participants (n) and percentage of participants (%) reporting the event by MedDRA SOC and PT.

Listings of AEs will include the date of onset, date of resolution (if AE is resolved) and investigator's assessment of severity, relationship to study drug, and NCI CTCAE grade. Separate listings will be produced for all AEs, SAEs, AESIs, AEs with outcome of death, AEs leading to discontinuation of acalabrutinib, AEs leading to discontinuation of study. Listings of AESIs will also include the additional information (eg, intervention, dose, duration of therapy etc.) recorded for these AEs. All AEs that are not treatment-emergent will be flagged in the data listings and the time of onset will be flagged as 'pre-treatment', 'post-treatment and no other anti-cancer therapy' and 'after initiation of other anti-cancer therapy'.

An overview AE summary table will be provided which will include the number of participants with grade ≥ 3 AEs, SAEs, AESIs, AEs that lead to discontinuation of treatment and ECIs. In addition, AEs will be summarized for the following categories, and will be tabulated by preferred term in descending frequency, unless otherwise specified:

- All TEAEs by SOC and preferred term
- All treatment-related TEAEs
- TEAEs with maximum CTCAE grade 3 or higher
- TEAEs with maximum CTCAE grade 3 or higher, causally related to acalabrutinib
- All Serious TEAEs
- All treatment-related Serious TEAEs
- TEAEs that lead to discontinuation of acalabrutinib
- Treatment-related TEAEs that lead to discontinuation of acalabrutinib
- All AESIs
- All ECIs

For each of these categories, summaries will be presented for the TN cohort, R/R CLL cohort, prior ibrutinib therapy cohort and overall.

Treatment-related AEs are those judged by the investigator to be at least possibly related to the study drug (with a cause related to the study drug indicated on the Case Report Form (CRF)).

Death will be listed and summarized by cause of death.

The adverse event outputs tables may be repeated for participants with confirmed/suspected COVID-19 infection.

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4.3.3 Clinical Laboratory Tests

Laboratory data obtained up until the 30-day safety follow-up visit will be included in the summary tables for participants in the SAF. For all continuous hematology, lymphocyte subsets (T/B/NK) and clinical chemistry laboratory parameters, descriptive statistics will be produced for each test result in SI units, and absolute values, change from baseline will be summarized presented in box plot by analysis visit.

Shift tables for change in grade from baseline by worst CTC grade will be produced. The laboratory parameters for which CTC grade shift outputs will be produced are:

- Hematology: white cells count, hemoglobin, platelets, absolute neutrophil count (ANC), and lymphocytes (absolute count).
- Clinical chemistry: albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, bicarbonate, blood urea nitrogen, calcium, creatinine, glucose, lactate

dehydrogenase, magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin, and uric acid.

Figures of absolute value and change from baseline for selected parameters will be plotted over time as appropriate.

For all participants with baseline and any post-baseline absolute lymphocyte count (ALC) measurements, the summary of ALC at peak and time to peak ALC will be provided. Duration of lymphocytosis will be defined as the duration of time from the earliest date on which the ALC value met the lymphocytosis criteria at a post-baseline assessment to the earliest date on which a subsequent ALC value met the resolution criteria. ALC values will be listed for participants who developed lymphocytosis.

Serum immunoglobulin variables (IgA, IgG, and IgM) will be summarized at each scheduled post-baseline assessment. Participants who received intravenous immunoglobulins (IVIG) on the study will be excluded from the summary for IgG.

The number and percentage of participants who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each lab parameter. Abnormal laboratory parameters that are clinically significant and occur after the first dose of acalabrutinib will be reported as an AE.

Listings will be generated for treatment emergent abnormalities in both haematology and chemistry lab parameters per CTCAE grade.

4.3.4 Hy's law

Additional analysis of participants meeting select laboratory criteria will be performed to check for evidence of potential Hy's law. Laboratory parameters to assess Hy's law include; Alanine aminotransaminase (ALT), Aspartate aminotransaminase (AST), Total bilirubin (TBILI). The number and percent of participants achieving any of the following endpoints at least once post-baseline will be reported:

- $ALT \geq 3 \times \text{upper limit of normal (ULN)}$
- $AST \geq 3 \times \text{ULN}$
- $TBILI \geq 2 \times \text{ULN}$
- $ALT \text{ or } AST \geq 3 \times \text{ULN, and } TBILI \geq 2 \times \text{ULN at the same visit}$

A listing including all reported ALT, AST, TBILI results will be provided for any participants with ALT or AST $> 3 \times \text{ULN}$.

4.3.5 Electrocardiograms

ECG data will be listed only.

Abnormal ECGs that are clinically significant and occur after the first dose of acalabrutinib will be reported as an AE.

4.3.6 Vital Signs

Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be summarized by study visit for the SAF. A box plot of absolute values will also be produced by visit.

4.3.7 Concomitant Medications

All concomitant medications (see Section 7.7.2 of the CSP and section 3.3.3 of the SAP) will be summarized by ATC class and preferred term for the SAF and repeated for participants with confirmed/suspected COVID-19 infection. Concomitant procedures will be summarized by SOC and preferred term.

Participants with the same concomitant medication/procedure multiple times will be counted once per medication/procedure. A medication/procedure that can be classified into more than one chemical and/or therapeutic subgroups will be presented in each subgroup.

4.3.8 ECOG Performance Status

A shift table of ECOG Performance Status from baseline to worst post-baseline value will be provided for participants in the SAF.

A summary table of ECOG performance score by visit and overall will be presented. The ECOG performance score ranges from:

- 0 - Full activity
- 1 - Restricted activity
- 2 - In bed = 50% of the time
- 3 - In bed > 50% of the time
- 4 - 100% disabled

4.4 Analysis of Efficacy Data

The efficacy analyses will be conducted separately by cohort on the SAF. All cohorts will be separately assessed for response by the investigator according to iwCLL 2018 criteria ([Hallek, et al. 2018](#)). In addition, efficacy endpoints will be summarized by the subgroups defined in Section 4.3.2.

4.4.1 Overall Response

Overall response is defined as a participant's best overall response to the treatment (see Section 3.2.1).

ORR will be summarized together with its associated exact 95% confidence interval.

Participants without a post-baseline assessment will be included in the 'Missing' category.

Efficacy response data will be listed for the SAF.

4.4.2 Duration of Response (DOR)

KM estimates of the Q1, median and Q3 DOR and DOR at 3, 6, 9, 12, 18, 24, 32, 36, 42, 48, and 54 months will be presented with the appropriate two-sided 95% CIs. A plot of the KM DOR curve will be produced. A descriptive summary of time to response in participants who achieved CR, CRi or PR will also be provided.

4.4.3 Progression Free Survival (PFS)

KM estimates of the 10th percentile, Q1, median and Q3 PFS and PFS at 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, and 54 months will be presented with the appropriate two-sided 95% CIs. A plot of the KM PFS curve will be produced.

A sensitivity analysis will be performed censoring COVID-19 deaths.

4.5 Analysis of Patient-Reported Outcomes Data

The analyses of PRO data will be conducted on participants in the SAF.

4.5.1 EORTC-QLQ-C30

Summary measures of compliance and evaluability over time for the EORTC QLQ-C30 questionnaire and of clinically significant changes (improvement, deterioration) for each scale/item score (global health status/QoL, five functions and all symptoms) will be presented by cohort and visit.

Summaries of absolute value and change from baseline for each EORTC-QLQ-C30 scale/item will be presented overall and by cohort at each visit. Change from baseline will be analysed using a restricted maximum likelihood (REML) based repeated measures approach mixed model. The model will include but not limited to fixed categorical effects for cohort, visit and cohort-by-visit interaction. The baseline of each EORTC-QLQ-C30 scale/item and the baseline-by-visit interaction will be included as fixed covariates in the model. An unstructured covariance structure should be attempted first. If this fails to converge then the AR(1) structure will be applied.

4.5.2 PRO-CTCAE

The PRO-CTCAE for each item and attribute (frequency, severity and/or interference) will be presented by assessment timepoint using summaries and descriptive statistics. The proportion of missing data will be included in the 'Missing' category.

4.6 Analysis of Pharmacokinetic Data

PK results will be summarized and reported for the PKAS.

Descriptive statistics (n, mean, SD, %CV, median, minimum, maximum) of plasma concentrations of acalabrutinib and its metabolite (ACP-5862) will be presented by treatment cohort and visit.

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

Additional Population PK analyses to be performed will be provided in a separate PK analysis plan if applicable.

5 INTERIM ANALYSES

No formal statistical comparisons will be carried out in this single-arm trial or interim analyses.

An interim analysis will be performed when approximately 100 participants complete 12 cycles of acalabrutinib to identify early safety signals and minimize the risk to participants. Additionally, this study will be monitored on an on-going basis by the sponsor and will have periodic assessments performed by the Data Safety Monitoring Committee (DSMC).

The following tables will be produced:

- Summaries of participant disposition, protocol deviations, analysis sets
- Summary of demographic and baseline characteristics and exposure to Study Drug
- Overall summary of TEAEs
- Summary tables of safety lab and vital sign.

6 CHANGES OF ANALYSIS FROM PROTOCOL

There is no change of the analysis with respect to the protocol.

7 REFERENCES

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8 APPENDIX

Appendix 1. Schedule of Assessments

	Screening Visit	Study Intervention Period (up to 48 cycles) (each cycle is 28 days) ^a				30-day Safety Follow-up visit	Disease Follow-up ^b	Post DCO ^c
		Cycle 1 Day 1 (±3 days)	Cycle 2 Day 1 (±3 days)	Cycle 3-6 Day 1 (±3 days)	Cycles 7-48 Day 1 (±7 days)	~30 days from last dose of study intervention (+7 days) ^d	q24w after completion of 48 cycles for participants who remain on study intervention (±14 days) until the final DCO	
Confirm eligibility	X				-			-
Informed consent	X				-			-
Acalabrutinib administration/dispensation ^e	-	Continuous 100 mg bid PO dosing				- ^b		-
Demographics, medical history and prior medications ^f	X				-			-
CIRS ^g	X				-			-
Physical examination ^h	X	X	X	X	X ⁱ	X	X	-
Disease-related symptoms ^j	X	X	X	X	X ⁱ	X	X	-
Vital signs ^k	X	X	X	X	X ⁱ	X	X	-
ECOG performance status	X	X	X	X	X ⁱ	X	-	-

	Screening Visit	Study Intervention Period (up to 48 cycles) (each cycle is 28 days) ^a				30-day Safety Follow-up visit	Disease Follow-up ^b	Post DCO ^c
		Cycle 1 Day 1 (±3 days)	Cycle 2 Day 1 (±3 days)	Cycle 3-6 Day 1 (±3 days)	Cycles 7-48 Day 1 (±7 days)	~30 days from last dose of study intervention (+7 days) ^d	q24w after completion of 48 cycles for participants who remain on study intervention (±14 days) until the final DCO	
CT/MRI scan ^l	X	-	-	-	X (1 year after initial dose of study intervention)	-		-
BM biopsy and aspirate ^m	-	-	-	-	X (1 year after initial dose of study intervention)	-		-
ECG ⁿ	X	Only if clinically indicated				X	-	-
Pregnancy test ^o	X	X	X	X	X	X	X	-
Hematology ^p	X	X	X	X	X	X	-	-
Serum chemistry ^q	X	X	X	X	X	X	-	-
Creatinine clearance	X	X	X	X	X	X	-	-
Hepatitis serology ^r	X	-	-					-
HBV PCR ^r	X	-	-	-	-	X ^r		-
HCV PCR ^s	X	-	-					-

	Screening Visit	Study Intervention Period (up to 48 cycles) (each cycle is 28 days) ^a				30-day Safety Follow-up visit	Disease Follow-up ^b	Post DCO ^c
		Cycle 1 Day 1 (±3 days)	Cycle 2 Day 1 (±3 days)	Cycle 3-6 Day 1 (±3 days)	Cycles 7-48 Day 1 (±7 days)	~30 days from last dose of study intervention (+7 days) ^d	q24w after completion of 48 cycles for participants who remain on study intervention (±14 days) until the final DCO	
Serum immunoglobulins, T/B/NK/monocyte counts ^t	X	-	-	X Cycle 6	X q6 cycles	-		-
Beta-2-microglobulin ^t	X	-	-	X Cycle 6	X q6 cycles	-		-
FISH, TP53 mutation, IGHV, and karyotyping ^u	X	-	-			-	-	-
Overall response assessment ^v	-	-	-	-	X (1 year after initial dose of study intervention)	-		
Concomitant medications ^w	X	X	X	X	X	X	X	-
Adverse events ^x	X	X	X	X	X	X	X	X ^c
Survival status ^y	-	X				X	X	X ^c
Disease progression	-	X				X	X	-
EORTC-QLQ-C30 ^z	-	X	X	X	X	-	-	-
PRO-CTCAE ^z	-	X	X	X	X	-	-	-

	Screening Visit	Study Intervention Period (up to 48 cycles) (each cycle is 28 days) ^a				30-day Safety Follow-up visit	Disease Follow-up ^b	Post DCO ^c
		Cycle 1 Day 1 (±3 days)	Cycle 2 Day 1 (±3 days)	Cycle 3-6 Day 1 (±3 days)	Cycles 7-48 Day 1 (±7 days)	~30 days from last dose of study intervention (+7 days) ^d	q24w after completion of 48 cycles for participants who remain on study intervention (±14 days) until the final DCO	
Pharmacokinetics ^{aa}	-	-	-	X ^{bb}	X ^{bb}	-	-	-
Target/non-target lesion assessments ^{cc}	-	X	X	X	X ^{dd}	-	-	-
Urinalysis ^{ee}	X							-

- a) From Cycle 1 to Cycle 6, in-clinic visits will occur every cycle, and from Cycle 7 to Cycle 48, in-clinic visits will occur every 3 cycles.
- b) If a participant continues to derive benefit from treatment at the end of 48 cycles and prior to the final DCO, they will continue to be provided with study intervention and will be followed in the Disease Follow-up period q24w until study intervention discontinuation due to, for example, disease progression or toxicity, withdrawal of consent, loss to follow-up, death, or study termination by the sponsor, whichever occurs first. After the final DCO, 2 options will be considered: participants may be transitioned to another study or may shift to a commercial supply of acalabrutinib/off-study acalabrutinib, if available and as permitted by local regulation. Details are provided in Section 4.3 of the clinical study protocol. Participants who switch to off-study acalabrutinib will be considered as having completed the study and therefore will not have any additional study assessments, including the SFU visit and the Disease Follow-up period. They will follow the standard of care in that country.
- c) For participants whose treatment is ongoing at the time of the final DCO, 2 options will be considered: participants may be transitioned to another study or may shift to a commercial supply of acalabrutinib / off-study acalabrutinib as permitted by local regulation. Only safety will be collected post-DCO. Safety data will be collected until the participant rolls over onto another study, begins commercial use, or is discontinued from study intervention. Participants who do not transition to another study or to a commercial supply of acalabrutinib/off-study acalabrutinib after the final DCO will be discontinued from study intervention and required to complete the 30-day SFU period.
- d) The SFU is no less than 30 days after last dose of study intervention. The 30-days Follow-up visit will be applicable only for those who discontinue the study medication for any reason before the final DCO post-48 cycles.

- e) The participant will be asked to take one 100 mg capsule orally, twice daily with 8 ounces (approximately 240 mL) of water. Study intervention to continue until start of new anti-CLL therapy or progression of CLL, or unacceptable toxicity, whichever occurs first. During in-clinic visits study medication should be dispensed to the participant. Between Cycle 7 and Cycle 48, participants will need to come to the study site every 3 cycles for study intervention dispensation where the compliance (including review of the participant's drug diary) and refill of study intervention will be performed. Post-48 cycles, the visit frequency and drug dispensation may change based on the investigator's discretion. The drug diary should be completed until the last dose of study intervention.
- f) Participant demographics and baseline characteristics will be collected. Complete medical history from the date of CLL diagnosis will include concurrent medical signs and symptoms, alcohol use and, if a smoker, cigarette use. History of substance abuse (tobacco in pack/year) and allergies should be recorded in the eCRF. Disease history, including the date of initial diagnosis, Rai or Binet staging within 28 days before first dose with study intervention, and history of autoimmune CLL complications and treatment will also be recorded based on available documents and participant history. Prior medications will be recorded in the eCRF.
- g) Cumulative Illness Rating Scale scoring is to be performed by a qualified licensed provider (eg, physician, physician's assistant, or nurse). This does not apply to participants in the UK, as participants will not be enrolled into the TN cohort of this study. Participants in the UK will be enrolled ONLY into the R/R cohort or the prior ibrutinib cohort.
- h) Physical examination will include height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal, nervous, and lymphatic system and general appearance. The lymphatic system examination will include bidimensional measurements of palpable lymph nodes and measurement of spleen and liver sizes by centimeters below the costal margin on the respective side. Only physicians, physician assistants, or oncology nurse practitioners should perform the lymphatic system examination. As much as possible, the same person should perform all the lymphatic examinations for a given participant. Abnormal physical examination findings that are clinically significant and occur after the first dose of study intervention up to 30 days after the last dose of study intervention will be reported as an AE.
- i) Starting with Cycle 7, assessment will be done every 3 cycles through Cycle 12. Starting at Cycle 13, assessment will be done every 6 cycles.
- j) Disease-related symptoms will be assessed and recorded in the participant records and are defined per [Hallek, et al. 2018](#) as: 1) unintentional weight loss of 10% or more within the previous 6 months; 2) significant fatigue (ie, ECOG performance status 2 or worse; inability to work or perform usual activities); 3) fevers higher than 100.5°F or 38°C for 2 or more weeks without other evidence of infection; or 4) night sweats for more than 1 month without evidence of infection.
- k) Vital signs (blood pressure, heart rate, respiratory rate, and either body or tympanic temperature) will be assessed after the participant has rested at least 5 minutes in the seated position. Abnormal vital sign findings that are clinically significant and occur after the first dose of study intervention up to 30 days after the last dose of study intervention will be reported as an AE.
- l) Radiologic imaging by CT with contrast is required and must include the pelvis, abdomen, chest, and neck (and any other disease area). Participants who are intolerant to intravenous CT contrast agents will have CT scans performed with oral contrast. MRI may be used for imaging assessments if a contrast CT scan is contraindicated or unobtainable. The imaging will be done at screening and at 1 year after initial dose of study intervention. Any additional imaging will be performed according to institutional standards.
- m) Bone marrow biopsies and aspirates to confirm a CR must be done within 4 weeks of the CT/MRI scan that showed suspected CR. If BM biopsy or aspirate was performed to confirm CR within the prior 90 days, then no additional biopsy or aspirate is necessary.
- n) Electrocardiograms will be performed at screening and SFU. Unscheduled ECGs should be performed at any time when clinically indicated. If an unscheduled ECG is done at any time, then an electrolyte panel (ie, calcium, magnesium, and potassium) must be done within 24 hours to coincide with the ECG testing. Participants should be in supine position and resting for at least 10 minutes before any study-related ECGs. Heart rate, PR, QRS, QT, and QTcF intervals will be recorded from the standard lead of the computerized quantitative 12-lead ECG measurement. Abnormal ECGs that are clinically significant and occur after the first dose of study intervention up to 30 days after the last dose of study intervention will be reported as an AE.

- o) Serum pregnancy testing for WOCBP will be done at study site at screening. Serum or urine pregnancy testing should be done at each cycle, during the Disease Follow-up period every 4 weeks, at the SFU visit, and at any point when it is clinically indicated. Continuous contraception (as per protocol) is required until 2 days after last dose of acalabrutinib. If the pregnancy test does not correspond with a clinic visit, an option for pregnancy testing between cycle visits can be an at-home urine pregnancy test followed by a phone call from site staff to confirm the results. Alternatively, a pregnancy test (serum or urine) can be done in the clinic. Follow-up phone calls will be made to the female participant to confirm the results of the at-home urine pregnancy assessments.
- p) Hematology assessments must include complete blood count with differential, including white blood cell count, hemoglobin, hematocrit, platelet count, absolute neutrophil count, and absolute lymphocyte count. Cycle 1 Day 1 hematology does not need to be repeated if screening hematology was done within 5 days. Assessment will be done every cycle through Cycle 6. After Cycle 6, assessments will be done every 3 cycles through Cycle 48. After Cycle 48, testing should be done per local practice per physician discretion.
- q) Serum chemistry must include albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, creatine kinase, glucose, LDH, magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid. If an unscheduled ECG is done at any time, then an electrolyte panel (ie, calcium, magnesium, and potassium) must be done within 24 hours to coincide with the ECG testing. Cycle 1 Day 1 serum chemistry does not need to be repeated if screening serum chemistry was done within 5 days. Assessment will be done every cycle through Cycle 6. After Cycle 6, assessments will be done every 3 cycles through Cycle 48. After Cycle 48, testing should be done per local practice per physician discretion.
- r) Hepatitis serology will include HBsAg, anti-HBs, anti-HBc, and anti-HCV. A positive test for hepatitis B or C by PCR at screening is an exclusion criterion for this study. Any participant who is both anti-HBc-positive and HbsAg-negative (which is possibly indicative of prior or chronic HBV infection) must have quantitative HBV DNA PCR testing performed during screening and on study. If the PCR testing is negative, these participants should receive prophylactic antiviral therapy (such as entecavir or tenofovir) and undergo monitoring with HBV DNA PCR q12w (or per institutional guidelines) during treatment and until 12 months after the last dose of study intervention. Any participant with a positive PCR test should discontinue all study intervention(s), have antiviral therapy instituted, and have a consultation with a physician with expertise in managing hepatitis B. Because IVIG may cause false-positive hepatitis serology, PCR testing q12w is not required in participants who are currently receiving or received prophylactic IVIG within 12 weeks before study enrollment and have a documented negative anti-HBc test before the initiation of IVIG therapy. PCR testing should be performed when clinically indicated (eg, in the setting of rising transaminase levels). Participants with a known history of hepatitis C or who are hepatitis C antibody positive should be tested for HCV RNA by PCR during screening. Participants should be excluded if PCR is positive. No further testing beyond screening is necessary if PCR results are negative.
- s) A positive test for hepatitis C by PCR at screening is an exclusion criterion for this study. Participants with a known history of hepatitis C virus or who are hepatitis C virus antibody positive should have hepatitis C virus PCR testing performed during screening. No further testing beyond screening is necessary if hepatitis C virus PCR results are negative.
- t) Whole blood samples will be analyzed for absolute T/B/NK counts (CD3+, CD19+, CD4+, CD8+, CD16+/56+ are mandatory, CD20, CD23, CD5 and polymphocytes as optional) using a standard cell marker panel. This assay will be performed on the same blood sample collected for standard hematology. Serum samples will also be analyzed for quantitative immunoglobulin (IgG, IgM, IgA) levels and serum β 2-microglobulin. In cases where participant tests COVID-19 positive, the investigator will assess the benefits/risks for study intervention intake versus COVID-19 treatment and the participant will continue on study intervention at the investigator's discretion. The participant will have tests for serum immunoglobulins levels after 2 months of COVID-19 infection cure.
- u) Peripheral blood (required) sample will be taken before the first dose of study intervention and sent for analysis within 60 days before or during screening for del(17p), del(13q), +12, and del(11q) by FISH (NGS/ Sanger sequence method, NGS method is preferred), TP53 mutation sequencing, and standard karyotyping. If these samples are damaged during collection or shipment, they should be redrawn at the next subsequent visit. Molecular analysis to detect IGHV mutation status will be done at screening only if not done at any time point before, since diagnosis.

- v) Response evaluations will be done at least 1 year after start of study intervention and per institutional guidelines. An unscheduled visit may be conducted if required as determined by the study site. Overall response assessments will include evaluation of physical examinations, recording of symptoms, BM biopsy and aspirate if radiological evaluation is indicative of a CR, and hematologic evaluations (Note: complete blood count with differential must be done within 7 days). Participants who have signs and symptoms of progression outside of the scheduled assessment should be evaluated by the investigator with a physical examination and a complete blood count with differential to determine if disease progression is present. Participants may continue study intervention until progression is confirmed by a serial examination at least 2 weeks later or until new CLL treatment is initiated, if considered clinically indicated by the investigator (must be discussed with the medical monitor). If additional response assessments are performed per institutional guidelines outside of the 1-year assessment, these must be recorded in the eCRF.
- w) Concomitant medications will be recorded from screening through 30 days after the last dose of study intervention. At cycles with no on-site visits, concomitant medication will be recorded via a telephone call.
- x) Adverse events (including SAEs, ECIs, and AESIs) will be collected from screening throughout the treatment period for all cycles and during the Disease Follow-up period. At cycles with no on-site visits, AEs will be collected and recorded via a telephone call.
- y) Each participant should be followed until one of the following occurs: study intervention discontinuation (eg, disease progression, toxicity), withdrawal of consent, loss to follow-up, death, or study termination by the sponsor, whichever comes first.
- z) If applicable for the country or region where the study is conducted, EORTC-QLQ-C30 should be done at baseline, then q4w for Cycles 1 through 6, and q8w thereafter until Cycle 48; PRO-CTCAE should be done at baseline, then weekly for the first 3 cycles, q4w for Cycles 4 through 6, and then q8w thereafter until Cycle 48. The time window for completion of both questionnaires is ± 2 days up to and including Cycle 3, then ± 7 days thereafter.
- aa) Pharmacokinetic samples will be collected 30 to 60 minutes before dosing and at 1 hour (± 15 minutes) after dosing. On the day of PK sampling, the participant will not take a dose of any study intervention before arrival at the clinic. Dosing will be observed by the clinic staff.
- bb) Performed on Cycle 3 Day 1 and Cycle 15 Day 1 only.
- cc) Target lesions are lymph nodes that are followed for response assessments. Non-target lesions refer to additional lymph nodes under surveillance.
- dd) To be performed on Cycle 9 Day 1, Cycle 12 Day 1 and thereafter every 6 cycles (Cycles 18, 24, 30, 36, 42, and 48) and 1-year response evaluation, per standard institutional practice and at investigator discretion, as clinically indicated.
- ee) To be performed unscheduled on any visit, only if required.

Note: Additional assessments may be made based on clinical judgment and institutional guidelines. For this study, participants in the UK will be enrolled ONLY into the R/R cohort or the prior ibrutinib cohort. Participants in the US will be enrolled ONLY into the TN or R/R cohort.

AE = adverse event; AESI = adverse event of special interest; anti = antibody; anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; anti-HCV = hepatitis B antibody; bid = twice daily; BM = bone marrow; CD = cluster of differentiation; CIRS = Cumulative Illness Rating Scale; CLL = chronic lymphocytic leukemia; CR = complete response; CT = computed tomography; DCO = data cutoff; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECI = event of clinical interest; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EORTC-QLQ-C30 = European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30; FISH = fluorescence in situ hybridization; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; Ig=immunoglobulin; IGHV = immunoglobulin heavy-chain variable, IVIG = intravenous immunoglobulins; iwCLL = International Workshop on Chronic Lymphocytic Leukemia; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; NGS = next-generation sequencing; NK = natural killer; PCR = polymerase chain reaction; PK = pharmacokinetic; PO = per os (by mouth); PRO-CTCAE = Patient-reported Outcomes version of the Common Terminology Criteria for Adverse Events; q4w = every 4 weeks; q8w = every 8 weeks; q12w = every 12 weeks; q24w = every 24 weeks; QTcF = corrected QT interval using Fridericia's formula; R/R = relapsed/refractory; RNA = ribonucleic acid; SAE = serious adverse event; SFU = safety Follow-up visit; TN = treatment-naïve; WOCBP = women of childbearing potential.

Appendix 2. Complete list for Events of Clinical Interest

I. 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

PT=preferred term.

II. Events of Clinical Interest (ECIs)

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. The "Additional (to Primary) Criteria for Narratives" listed in the last column of the table below would be used only for narratives purpose (not for ECI programming logic).

Category	Subcategory	Definition	Additional (to Primary) Criteria for Narratives
Cardiac events		• SOC Cardiac disorders	No additional criteria
	Atrial fibrillation	• PT Atrial fibrillation • PT Atrial flutter	Grade 3 and 4
	Ventricular arrhythmia	• PT Torsade de pointes • PT Ventricular arrhythmia • PT Ventricular extrasystoles • PT Ventricular fibrillation • PT Ventricular flutter • PT Ventricular tachyarrhythmia • PT Ventricular tachycardia	Any
Cytopenias – Anemia		• SMQ Haematopoietic erythropenia [narrow + broad]	No additional criteria
Cytopenias – Leukopenia		• SMQ Haematopoietic leukopenia [narrow + broad]	No additional criteria
	Neutropenia	• PT Band Neutrophil count decreased • PT Cyclic neutropenia • PT Febrile Neutropenia • PT Granulocyte count decreased • PT Idiopathic neutropenia • PT Neutropenia • PT Neutropenic infection	No additional criteria

Category	Subcategory	Definition	Additional (to Primary) Criteria for Narratives
		- PT Neutropenic sepsis - PT Neutrophil count decreased - PT Neutrophil percentage decreased	
	Other leukopenia	SMQ Haematopoietic leukopenia [narrow + broad] excluding PTs for neutropenia above	No additional criteria
Cytopenias - Thrombocytopenia		SMQ Haematopoietic thrombocytopenia [narrow + broad]	No additional criteria
Hemorrhage		SMQ Haemorrhage terms (excl laboratory terms)	No additional criteria
	Major hemorrhage	As per definition (see Section 3 below)	Any
Hepatotoxicity		- SMQ Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions[narrow] - excluding PT Spontaneous bacterial peritonitis. - SMQ Hepatitis, non-infectious[narrow] - SMQ Liver related investigations signs and symptoms [narrow]	Participants who fulfill biochemical Hy's law criteria defined as below: > 3 x ULN AST or > 3 x ULN ALT and > 2 x ULN total bilirubin at the same visit
Hypertension		SMQ Hypertension [narrow]	No additional criteria
Infections		- SOC Infections and infestations - SMQ Opportunistic infections - SMQ COVID-19	No additional criteria
Interstitial lung disease/Pneumonitis		SMQ [narrow] Interstitial lung disease	No additional criteria
Second primary malignancies		- SMQ Malignant tumours (including SMQ Haematological malignant tumours [narrow] and SMQ Non-haematological malignant tumours [narrow]) - SMQ Malignant lymphomas [narrow] - SMQ Myelodysplastic syndrome [narrow]	No additional criteria
	Second primary malignancies (excluding non-melanoma skin)	The above excluding PTs mapping to HLT Skin neoplasms malignant and unspecified (excluding melanoma)	Any
Tumor lysis syndrome		PT Tumour lysis syndrome	Any

AE=adverse event; ALT= alanine aminotransferase; AST=aspartate transaminase; CSP=clinical study protocol; PT=preferred term; HLT=high level term; SMQ=Standardized MedDRA Queries; SOC=system organ class;

Most recent version of MedDRA

'No additional criteria' means only SAE, AE leading to study drug discontinuation, and deaths within specified window will be selected for narratives.

‘Any’ means any participant with a PT in the category will be selected for narratives.

III. 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

- Basal ganglia haematoma
- Basal ganglia haemorrhage
- Brain stem haematoma
- Brain stem haemorrhage
- Brain stem microhaemorrhage
- Central nervous system haemorrhage
- Cerebellar haematoma
- Cerebellar haemorrhage
- Cerebellar microhaemorrhage
- Cerebral arteriovenous malformation haemorrhagic
- Cerebral cyst haemorrhage
- Cerebral haematoma
- Cerebral haemorrhage
- Cerebral microhaemorrhage
- Encephalitis haemorrhagic
- Epidural haemorrhage
- Extradural haematoma
- Extracerebral cerebral haematoma
- Haemorrhage intracranial
- Haemorrhagic cerebral infarction
- Haemorrhagic stroke
- Haemorrhagic transformation stroke
- Intracerebral haematoma evacuation

- Intracranial haematoma
- Intracranial tumour haemorrhage
- Intraventricular haemorrhage
- Meningorrhagia
- Optic disc haemorrhage
- Optic nerve sheath haemorrhage
- Pituitary apoplexy
- Pituitary haemorrhage
- Putamen haemorrhage
- Spinal cord haematoma
- Spinal cord haemorrhage
- Spinal epidural haematoma
- Spinal epidural haemorrhage
- Spinal subarachnoid haemorrhage
- Spinal subdural haematoma
- Spinal subdural haemorrhage
- Spontaneous subdural haematoma
- Subarachnoid haematoma
- Subarachnoid haemorrhage
- Subdural haematoma
- Subdural haematoma evacuation
- Subdural haemorrhage
- Thalamus haemorrhage
- Traumatic intracranial haematoma
- Traumatic intracranial haemorrhage

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