

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

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Clinical Study Protocol

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

TITLE PAGE

Sponsor:

AstraZeneca
AstraZeneca AB, S-151 85
Sodertalje, Sweden

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VERSION HISTORY

Amendment 4, Version 5.0 (Global), 25 August 2023
Addendum 1 (Finland), 30 May 2023
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Amendment 3, Version 4.0 (US), 20 December 2022
Amendment 3, Version 4.0 (UK), 20 December 2022

Amendment 3, Version 4.0 (Global), 20 December 2022
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Amendment 1, Version 2.0 (Global), 13 August 2019
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Original, Version 1.0, 12 February 2019

This clinical study protocol has been subject to a peer review according to the sponsor's standard procedures. The clinical study protocol is publicly registered and the results are disclosed and/or published according to the sponsor's global policy on bioethics and in compliance with prevailing laws and regulations.

SUMMARY OF AMENDMENT 4, 25 AUGUST 2023

This modification contains both substantial and non-substantial changes based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the EU and in the EU Clinical Trial Regulation Article 2, 2 (13).

Overall Rationale for the Amendment: The protocol has been amended to align with the latest safety data and standards for acalabrutinib. This protocol consolidates all previous versions, including country-specific protocols and addendums. Other changes for maintaining consistency within the protocol have been made.

List of Substantial Modifications

Section number and name	Description of change	Brief rationale
Section 1.4 Study Design Section 2.3 Exploratory Objectives Section 8.5.1 Efficacy Analyses	CCI [REDACTED]	CCI [REDACTED]

Section number and name	Description of change	Brief rationale
Section 9.3 Study Timetable and End of Study		CCI
Section 6.1 Risks Associated with Acalabrutinib Appendix L Regulatory and Ethical Considerations	- Specified the IB and current local labels as the sources for the full details on the clinical safety associated with acalabrutinib - Updated sources for consensus of ethical principles	Clarification Update required to comply with regulatory requirements (eg, EU Clinical Trial Regulation) and global company requirements
Appendix H Response Assessment Criteria (Modified from Hallek et al. 2018)	- Updated table of response definitions after treatment for CLL patients to address 2 typographical errors: 1 in the table on hemoglobin criteria for SD and 1 in the footnotes below the table for the criteria for partial remission - Added text on constitutional symptoms, complete response, complete response with incomplete marrow recovery, partial response, nodular partial remission, stable disease, and progressive disease	Alignment with the latest Hallek Criteria 2018 CLL Response Assessment Criteria

List of Non-Substantial Modifications

Section number and name	Description of change	Brief rationale
Global	- Updated all applicable instances of “Investigator” to “investigator” - Updated all applicable instances of “subject” to “participant” - Updated all applicable instances of “study drug” or “study treatment” to “study intervention”	General update to align with most recent formal institutional guidance and templates
Clinical Study Protocol Synopsis	The information in the Synopsis was amended in line with the edits in the body of the Clinical Study Protocol	Updated information

Section number and name	Description of change	Brief rationale
Section 1.2 Rationale for Study Design, Doses, and Control Groups Section 1.4 Study Design Section 3.1 Inclusion Criteria Section 3.3 Participant Enrollment Section 3.9.1 Dose Modification Section 3.9.2.1 Temporary Discontinuation Section 4 Study Plan and Timing of Procedures, Table 3 Section 4.1 Screening/Enrollment Period Section 4.1.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis Section 5.3.3 Cumulative Illness Rating Scale Section 8.2 Sample Size Estimate Appendix M Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis	- Added that participants in the UK will only be enrolled into the R/R cohort or prior ibrutinib cohort - Added that participants in the US will only be enrolled into the TN or R/R cohort - Added that guidance on study conduct mitigation in Germany only applies to the COVID-19 pandemic - Added that for the Republic of South Korea, hematology, serum chemistry, and creatinine clearance must be performed within 7 days of C1D1 and all other tests will be performed within the screening window of 28 days - Added that for Germany, study intervention may be held for a maximum of 28 consecutive days from expected dose due to toxicity of study disruptions due to the COVID-19 pandemic	Clarification and alignment with versions and addendums for different countries
Section 1.4 Study Design, Figure 1 Section 4 Study Plan and Timing of Procedures, Table 3 Section 4.2 Treatment Period (up to 48 Cycles) Section 4.3 Post-Treatment Period, Figure 2	- Updated text describing timing of some assessments to occur every 3 cycles from Cycle 7 to Cycle 12 - Updated text describing timing of assessments to occur after the first dose of study intervention up to 30 days after the last dose of study intervention or until the end of Disease Follow-up	Clarification of previous language
Section 3.2 Exclusion Criteria	- Updated Exclusion Criterion 4 to note that it is applicable to all 3 cohorts in Finland and the Republic of South Korea - Updated Exclusion Criterion 4 to note that participants in the US will not be enrolled in the prior ibrutinib cohort	Clarification and alignment with versions and addendums for different countries

Section number and name	Description of change	Brief rationale
Section 3.8 Drug-drug Interaction, Table 1	Updated “No dose adjustment. Monitor patients closely for adverse reactions if taking moderate CYP3A inhibitors” to “Reduce dose to 100 mg once daily”	Alignment with the latest safety data and standards
Section 3.9.2 Discontinuation from Study Intervention Section 3.10 Withdrawal from Study Section 4 Study Plan and Timing of Procedures, Table 3 Section 4.3 Post-treatment Period Section 6.5.1 Time Period for Collection of Adverse Events	- Updated text to remove instructions for following up with participants who discontinue treatment and do not agree to the SFU visit - Updated text to remove instructions for modified SFU options - Removed Discontinuation Follow-up row from Table 3 - Updated footnote x to specify AE collection will continue during the Disease Follow-up period - Updated details of follow-up after 48 cycles for participants in the Disease Follow-up period	Clarification of updated follow-up process
Section 4 Study Plan and Timing of Procedures, Table 3 Section 4.1 Screening/Enrollment Period Section 4.2 Treatment Period (up to 48 Cycles) Section 4.3 Post-treatment Period Section 5.1.1 Response Section 5.2.5 Pregnancy Testing Section 5.2.6 Concomitant Medications	- Updated 30-day Safety Follow-up visit to occur 30 days from last dose of study intervention - Added disease-related symptoms, concomitant medications, and pregnancy test to be required during Disease Follow-up - Added survival status to be required during the 30-day SFU - Clarified timing of bone marrow biopsy and aspirate - Added urinalysis assessment to all cycles, only as required - Added “or until new CLL treatment is initiated, if considered clinically indicated by the investigator (must be discussed with the medical monitor)” to footnote v - Updated footnote cc to provide definition of target and non-target lesions - Updated footnote dd to include standard institutional practice and investigator discretion of lesion assessments during Cycles 9 through 48, as clinically indicated	Clarification and elaboration of operational aspects of the study

Section number and name	Description of change	Brief rationale
	- Updated timing and details of pregnancy testing - Added text that positive test for hepatitis B or C by PCR at screening is an exclusion criterion to footnotes r and s - Removed statement that procedures conducted as part of the participant's routine clinical management obtained before signing the ICF may be used for screening or baseline purposes - Removed statement that blood samples for response or disease progression determination are to be confirmed	
Section 4 Study Plan and Timing of Procedures, Table 3 Section 5.1.2 Survival	Updated text on participant follow-up	Clarification
Section 4 Study Plan and Timing of Procedures, Table 3 Section 5.1.3.3 Administration of Patient-reported Outcomes Questionnaires	Added that ePROs will be completed until the end of Cycle 48	Clarification
Section 4 Study Plan and Timing of Procedures, Table 3 Section 5.2.2 Laboratory Safety Assessments	Added creatine kinase to the list of required serum chemistry parameters	Alignment with the latest safety data and standards
Section 4 Study Plan and Timing of Procedures, Table 3 Section 5.2.3 Electrocardiograms	Added directions for electrolyte panels if unscheduled ECGs are performed	Clarification

Section number and name	Description of change	Brief rationale
Section 4 Study Plan and Timing of Procedures, Table 3 Section 5.2.6 Concomitant Medications	- Updated footnote w from “Concomitant medications and anticancer therapies or procedures will be recorded from start of study treatment administration through 30 days after the last dose of study treatment. At cycles with no on-site visits concomitant medication will be recorded via a telephone call” to “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.” - Updated the heading title from “Concomitant Medications and Subsequent Anticancer Therapies” to “Concomitant Medications” - Deleted the text regarding the collection of participant concomitant medications beyond those defined in the SoA	Clarification General update for alignment and clarification
Section 4 Study Plan and Timing of Procedures, Table 3 Section 5.3.5 Physical Examination	Added that abnormal, clinically significant physical examination findings should be reported as AEs if they occur after the first dose of study intervention up to 30 days after the last dose of study intervention	Clarification
Section 4 Study Plan and Timing of Procedures, Table 3 Section 7.5 Compliance	- Added text stating that compliance included a review of the participant’s drug diary - Added text requiring drug diary completion through the last dose of study intervention	Clarification
Section 5.3 Other Assessments	Added “All protocol-required assessments must be conducted as defined in the SoA (see Table 3)”	General update to align with most recent formal institutional guidance and templates
Section 6.1.2.4 Second Primary Malignancies	Changed “non-melanoma skin carcinoma” to “non-skin carcinomas”	General update to align with most recent formal institutional guidance and templates

Section number and name	Description of change	Brief rationale
Section 6.1.3.1 Hepatotoxicity	Added clarifying verbiage to important potential risk of hepatotoxicity	Alignment with the latest safety data and standards
Section 6.4 Definition of Events of Clinical Interest Section 6.5.1 Time Period for Collection of Adverse Events Section 6.5.2 Follow-up of Unresolved Adverse Events Section 6.5.3 Variables Section 6.6.1 Reporting of Serious Adverse Events Section 6.6.2 Adverse Events of Special Interest Appendix B Further Guidance on the Definition of Adverse Events of Special Interest and Events of Clinical Interest	- Restructured and clarified AE, SAE, and AESI collection, reporting, and follow-up activities - Restructured description of AESIs and list of specific AESIs - Restructured how ECIs are described - Added subsection title for Section 6.6.1 Reporting of SAEs and added Section 6.6.2 Adverse Events of Special Interest - Removed former Appendix B to avoid duplication of material	General update to align with most recent formal institutional guidance and templates
Section 8.2 Sample Size Estimate Table 6	Updated table title to “Incidences of Safety Events in Participants with CLL Treated With Acalabrutinib (Study ACE-CL-001)”	Clarification
Section 8.5.1 Efficacy Analyses	Updated time of right-censoring of some participants to be DCO	Clarification
Section 8.5.2 Safety Analyses	Updated one definition of resolution of lymphocytosis to be achievement of an ALC value ≤ 5000 cells/ μ L	Clarification
Section 8.5.6 Interim Safety Analysis	Added text on timing of ISAs	Clarification
Section 10.2 Participant Data Protection	Updated period for retaining records and documents to 25 years after study archiving or as required by local regulation	General update to align with most recent formal institutional guidance and templates
Section 10.4 Informed Consent	Added text to clarify the use of participant coded data and biosamples	Clarification
Appendix A Additional Safety Information	Updated criteria for tumor-related SAEs	Clarification

Section number and name	Description of change	Brief rationale
Appendix L Regulatory, Ethical, and Study Oversight Considerations	• Updated text regarding data protection • Updated address of web page providing description of clinical study	Clarification
Appendix N Protocol Amendment History	Added summaries of changes from country-specific amendments and addendums	Clarification

CLINICAL STUDY PROTOCOL SYNOPSIS

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

International Coordinating Principal Investigator

Dr. Carsten Niemann, MD

Rigshospitalet, Copenhagen University Hospital
Department of Hematology
Blegdamsvej 9
DK-2100 Copenhagen Ø
Denmark

Medical Monitor

PPD

PPD

AstraZeneca
One Medimmune Way
Gaithersburg, MD, 20878, USA

Study Sites and Number of Participants Planned

Approximately 540 participants will be enrolled into this multicenter study at approximately 127 sites.

Phase of Development: IIIb

Study Design

This global, Phase IIIb, multicenter, open-label, single-arm study will evaluate the safety and efficacy of acalabrutinib 100 mg bid in approximately 540 participants with CLL. Participants will be enrolled into 3 cohorts: TN, R/R, and prior ibrutinib therapy.

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.

Objectives

Primary objective	Endpoints
To evaluate the safety and tolerability of acalabrutinib monotherapy in participants with treatment-naïve or relapsed/refractory chronic lymphocytic leukemia	Frequency, severity, and relatedness of all AEs, which will also include: - Grade ≥ 3 adverse events - Serious adverse events - Events of clinical interest 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 as defined in Section 6.4 - Adverse events of special interest defined as ventricular arrhythmias - Adverse events that lead to discontinuation of treatment
Secondary objective	Endpoints
To evaluate the investigator-assessed overall response, duration of response, and progression-free survival in participants receiving acalabrutinib monotherapy	Overall response Duration of response Progression-free survival

Target Participant Population

This study will enroll participants with treatment-naïve or relapsed/refractory CLL, or those who have received prior ibrutinib therapy for CLL and discontinued ibrutinib for any reason prior to disease progression.

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.

Treatment and Treatment Duration

Study intervention (acalabrutinib 100 mg) will be provided as hard, gelatin capsules for twice daily oral administration until completion of 48 cycles, study drug 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. Participants who benefit from the treatment and complete 48 cycles before the final DCO will continue to receive the study intervention until the final DCO.

Dose delays and modifications will be allowed. Study intervention may be held for a maximum of 28 consecutive days from expected dose due to toxicity, study disruptions due to cases of civil crisis, natural disaster, or public health crisis. During this period, appropriate laboratory monitoring should be performed per institutional guidelines, to whatever extent possible per protocol. Study intervention should be discontinued in the event of study intervention being held or being unavailable for > 28 days, unless reviewed and approved by the medical monitor (including in the Disease Follow-up period post-Cycle 48). For information on possible dose delays due to COVID-19, refer to [Appendix M](#).

If study intervention is reduced for apparent treatment-related toxicity, the dose need not be re-escalated, even if there is minimal or no toxicity with the reduced dose. However, if the participant tolerates a reduced dose of study intervention for ≥ 4 weeks then the dose may be increased to the next higher dose level, at the discretion of the investigator. Such re-escalation may be particularly warranted if further evaluation reveals that the AE that led to the dose reduction was not treatment-related.

Statistical Methods

In general, descriptive statistics (number of participants, mean, standard deviation, median, minimum, and maximum values) will be presented for continuous variables. Categorical variables will be summarized including the number and percentage of participants with non-missing data per category.

Analysis Populations

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

- **Safety Analysis Set (SAF):** participants who receive any dose 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. More details for participants included in statistical analysis of each specific efficacy endpoint will be provided in the SAP.
- **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.

Safety Analyses

Detailed tabulations of safety data will be provided for all participants receiving the study intervention. The number and percentage of participants with AEs, SAEs, AESIs, and ECIs, Grade ≥ 3 AEs, and AEs that lead to discontinuation of treatment will be summarized. Details will be provided in the SAP.

Efficacy Analyses

All cohorts will be separately assessed for response by the investigator according to iwCLL 2018 criteria ([Hallek et al. 2018](#)) and the OR rate in each group will be derived and will be presented with results including frequencies, percentages and 95% confidence interval using the Clopper-Pearson exact method. Kaplan-Meier methods will be used to estimate DOR and PFS.

Symptoms and health-related quality of life will be summarized according to the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 and Patient-reported Outcomes version of the CTCAE.

Pharmacokinetic Analyses

Plasma concentrations of acalabrutinib and ACP-5862 will be tabulated for each participant by visit and time point. Summary statistics (eg, mean, median, standard deviation, percent coefficient of variation) and plots will be presented, as appropriate. Additional analyses may be conducted by combining PK and other relevant data across studies. Potential correlations of exposure with safety and efficacy outcomes may be explored as warranted by the data. Details of the PK parameters and the analyses assessed are provided in the SAP.

Sample Size

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. (Participants in the UK will not be enrolled into the TN cohort. Participants in the US will not be enrolled into the prior ibrutinib therapy cohort.)

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study clinical study protocol.

Abbreviation or specialist term	Explanation
Ab	antibody
ANA	antinuclear antibody
ACP-196	acalabrutinib
ADL	activities of daily living
AE	adverse event
AESI	adverse events of special interest
ALC	absolute lymphocyte count
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
anti-HCV	hepatitis C antibody
ASCO	American Society of Clinical Oncology
ASMA	anti-smooth muscle antibody
AST	aspartate aminotransferase
BADL	basic activities of daily living
BCRP	breast cancer resistance protein
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
bid	twice daily
BM	bone marrow
BMI	body mass index
BPH	benign prostate hypertrophy
BR	bendamustine and rituximab
BTK	Bruton tyrosine kinase
BTKi	Bruton tyrosine kinase inhibitor
CD	cluster of differentiation
CD-transferrin	carbohydrate deficient transferrin
CFR	Code of Federal Regulations
CHF	congestive heart failure

Abbreviation or specialist term	Explanation
CI	confidence interval
CIOMS	Conference for International Organizations of Medical Sciences
CIRS	Cumulative Illness Rating Scale
c-LDL	low-density lipoprotein cholesterol
CLL	chronic lymphocytic leukemia
CMV	Cytomegalovirus
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CR	complete response
CRi	complete response with incomplete marrow recovery
CRO	clinical research organization
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	Clinical Trial Information System
CYP	cytochrome P450
DCO	data cutoff
del(11q)	11q deletion
del(13q)	13q deletion
del(17p)	17p deletion
DES	data entry site
DILI	Drug-Induced Liver Injury
DLBCL	diffuse large B-cell lymphoma
DNA	deoxyribonucleic acid
DOR	duration of response
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders
DSMC	data safety monitoring committee
DSUR	Development Safety Update Reports
DVT	deep venous thrombosis
EBV	Epstein Barr virus

Abbreviation or specialist term	Explanation
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDTA	ethylene diamine tetra-acetic acid
EENT	eyes, ears, nose and throat
EFD	embryofetal development
EMA	European Medicines Agency
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30
ePRO	electronic patient-reported outcome
EU	European Union
FCR	fludarabine, cyclophosphamide, and rituximab
FDA	Food and Drug Administration
FIMEA	Finnish Medicines Agency
FISH	fluorescence in situ hybridization
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GDS	Geriatric Depression Scale
GERD	gastroesophageal reflux disease
GGT	gamma glutamyl transferase
GI	gastrointestinal
HAV	hepatitis A virus
HBc	hepatitis B core
HBs	hepatitis B surface
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCP	health care professional
HCV	hepatitis C virus
HEV	hepatitis E virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HL	Hy's Law

Abbreviation or specialist term	Explanation
HR	hazard ratio
HSV	herpes simplex virus
IADL	instrumental activities of daily living
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	independent ethics committee
Ig	immunoglobulin
IGHV	immunoglobulin heavy-chain variable
IMP	investigational medicinal product
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IR/BR	idelalisib + rituximab/bendamustine and rituximab
IRC	Independent Review Committee
IRT	Interactive Response Technology
ISA	interim safety analysis
IV	intravenous
IVIG	intravenous immunoglobulins
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
IWWM-3	The Third International Workshop on Waldenström Macroglobulinemia
IWWM-6	The Sixth International Workshop on Waldenström Macroglobulinemia
KM	Kaplan-Meier
LDH	lactate dehydrogenase
LDT	lymphocyte doubling time
LKM	liver/kidney microsomal antibody
LN	lymph node
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MFDS	Ministry of Food and Drug Safety

Abbreviation or specialist term	Explanation
MI	myocardial infarction
MMSE	mini mental status exam
MRD	maximum recommended dose
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NIMP	non-investigational medicinal product
NK	natural killer (cells)
nPR	non-partial response
NSAID	non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
OR	overall response
ORR	objective response rate
PAD	peripheral artery disease
PB	peripheral blood
PCR	polymerase chain reaction
PD	progressive disease
PET-CT	positron emission tomography-computer-tomography
PFS	progression-free survival
PHL	Potential Hy's Law
PK	pharmacokinetic
PKAS	pharmacokinetic analysis set
PML	progressive multifocal leukoencephalopathy
PO	orally
PR	partial response
PRO	patient-reported outcomes
PRO-CTCAE	Patient-reported Outcomes version of the Common Terminology Criteria for Adverse Events
PT	preferred term
q4w	every 4 weeks

Abbreviation or specialist term	Explanation
q8w	every 8 weeks
q12w	every 12 weeks
q24w	every 24 weeks
qd	once daily
QTcF	corrected QT interval using Fridericia's formula
RNA	ribonucleic acid
R/R	relapsed/refractory
RTSM	Randomization and Trial Supply Management
SAE	serious adverse event
SAF	safety analysis set
SAP	Statistical analysis plan
SD	stable disease
SFU	safety Follow-up
SLL	small lymphocytic lymphoma
SoA	schedule of assessments
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TBL	total bilirubin
TIA	transient ischemic attack
TN	treatment-naïve
TP53	tumor protein 53
TPV	third-party vendor
TTNT	time to next treatment
TURP	transurethral resection of the prostate
UK	United Kingdom
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
UTI	urinary tract infection
WBC	white blood cell
WM	Waldenström Macroglobulinemia
WOCBP	women of childbearing potential

1 INTRODUCTION

1.1 Background and Rationale for Conducting This Study

1.1.1 Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia is the most prevalent form of adult leukemia, with an age-adjusted incidence of 3.3 to 6.4 per 100,000 person-years and a median age at diagnosis of 70 years, based on the population in the US (Noone et al. 2018). Treatment of CLL is often deferred in asymptomatic participants with early-stage disease and initiated once there is evidence for progressive or symptomatic disease (summarized as “active” disease) as defined by iwCLL (2018) guidelines (Hallek et al. 2018).

In participants without high-risk cytogenetics, for example, del(17p) or TP53 mutation, chemoimmunotherapy remains the standard of care as first-line therapy (NCCN 2018; Eichhorst et al. 2015). Randomized clinical studies have established the combination of FCR as frontline therapy in a younger population with few comorbidities. FCR can lead to prolonged PFS in a subset of participants. Specifically, best results are noted in participants without chromosome 17 abnormalities and with mutated IGHV gene. Older age (> 65 years) was associated with a lower rate of complete remission and increased likelihood of not completing the full 6 cycles because of persistent cytopenias (Tam et al. 2008). In one investigation, the ORR to FCR was 95%, with 72% CR; unfavorable-risk participants had a CR rate of 48%, with those having abnormal chromosome 17 achieving lower rates of CR (Tam et al. 2008). Minimal residual disease negativity in the bone marrow was achieved in 82% (flow cytometry) and 42% (PCR) of participants who achieved CR. Progression-free survival was 30.9% at 12.8 years, and median PFS was 6.4 years; among participants with mutated IGHV, 53.9% were still in remission (Thompson et al. 2016). The combination of BR is another standard of care option, especially for elderly participants or those with prior infections. In a head-to-head comparison of participants treated with BR versus FCR, median PFS was 41.7 months versus 55.2 months, respectively. participants treated with BR had a lower incidence of hematologic toxicity and infectious complications, thus BR is a viable option for elderly participants or those with prior infections (Eichhorst et al. 2015).

Despite the potential for prolonged PFS with chemoimmunotherapy, both FCR and BR are associated with significant short- and long-term toxicities. There currently exists a need for frontline chemotherapy-free regimens in participants with comorbidities that can offer improved outcomes with less toxicity.

1.1.2 Bruton Tyrosine Kinase Inhibition

Inhibition of BTK is a validated therapeutic and has established activity in CLL. Ibrutinib (IMBRUVICA®), a covalent BTKi, has demonstrated improved PFS and overall survival in participants with R/R or TN CLL as compared with conventional therapies (IMBRUVICA 2017). In addition to inhibition of BTKi, ibrutinib has also shown in vitro activity against other kinases (eg, epidermal growth factor receptor; Honigberg et al. 2010), which may contribute to treatment-related diarrhea and rash. The inhibition of interleukin-2-inducible T-cell kinase that is seen with ibrutinib has the potential to abrogate NK cell antibody-dependent cellular cytotoxicity (Kohrt et al. 2014), which makes combination with monoclonal antibodies less effective. In addition, ibrutinib is a substrate for both CYP enzymes 3A4/5, which increases the possibility of drug-drug interactions.

1.1.3 Acalabrutinib

Acalabrutinib (also known as ACP-196) is a selective, irreversible, small molecule inhibitor of BTK. Acalabrutinib is an approved drug for the treatment of adult patients with CLL/SLL, in both the treatment-naïve and R/R setting, and MCL who have received at least one prior therapy. Acalabrutinib is currently being investigated in clinical studies for B-cell malignancies.

Acalabrutinib produces high rates of durable response in participants with CLL and is well tolerated. In addition, laboratory studies have shown that acalabrutinib and its major metabolite, ACP-5862, have limited off-target kinase activity, inhibiting only 2 other related kinases (erb-b2 receptor tyrosine kinase 4 and bone marrow tyrosine kinase gene in chromosome X) at clinically relevant concentrations (Byrd et al. 2016a; Barf et al. 2017). The lack of activity against other Tec- and Src-family kinases, which are important for the function of T-cells, NK cells and platelets, and against epidermal growth factor receptor, a kinase important for epithelial cell functions, may contribute to the safety and efficacy profile of acalabrutinib.

As of 30 October 2021, more than 5000 participants have participated in acalabrutinib clinical studies, with approximately 4600 participants receiving acalabrutinib as monotherapy or in combination with other agents.

All available efficacy data for acalabrutinib monotherapy (100 mg bid) as well as efficacy data for the combination of acalabrutinib 100 mg bid with obinutuzumab from 2 pivotal Phase III studies in previously untreated CLL (Study ACE-CL-007; through the DCO date of 08 February 2019), and R/R CLL (Study ACE-CL-309; through the DCO date of 15 January 2019) are summarized.

Study ACE-CL-309 enrolled and randomized a total of 310 participants (15 January 2019), and all but 3 participants (1 in the acalabrutinib arm and 2 in the IR/BR arm) received study intervention. The median time on study for acalabrutinib and IR/BR participants was 16.1 months (range: 0.5 to 22.4 months) and 15.7 months (range: 0.0 to 22.1 months), respectively. Acalabrutinib demonstrated a 69% reduction in risk of IRC-assessed disease progression or death compared with IR/BR (HR = 0.31 [95% CI: 0.20, 0.49], $p < 0.0001$). The median estimated PFS for acalabrutinib was not reached; the median estimated PFS for IR/BR was 16.5 months (95% CI: 14.0, 17.1). The KM estimated 18-month PFS rates for acalabrutinib and IR/BR were 79.0% (95% CI: 69.7, 85.8) and 38.6% (95% CI: 27.3, 49.8), respectively. The key sensitivity analysis of PFS without censoring for subsequent anticancer therapy was consistent with the primary analysis and showed similar improvement in PFS for acalabrutinib compared with IR/BR (HR = 0.33; $p < 0.0001$). All other sensitivity analyses were also consistent with the primary analysis, confirming the robustness of the primary analysis. Analysis on the secondary endpoint of investigator-assessed PFS was consistent with primary analysis (HR = 0.28 [95% CI: 0.18, 0.45]; $p < 0.0001$). The clinical benefit with acalabrutinib was further demonstrated by a clinically relevant improvement in DOR for acalabrutinib compared with IR/BR, both by IRC assessment (HR = 0.33) and investigator assessment (HR = 0.20), and a significant prolongation of TTNT for acalabrutinib compared with IR/BR (HR = 0.35; $p < 0.0001$). ORR (CR + CRi + nPR + PR) for acalabrutinib and IR/BR was similar based on IRC assessment (81.3% and 75.5%, respectively) and investigator assessment (79.4% and 83.2%, respectively).

Study ACE-CL-007 enrolled and randomized a total of 535 participants (08 February 2019), and 526 participants (98.3%) were treated with at least one study intervention. The median time on study for acalabrutinib + obinutuzumab, acalabrutinib monotherapy, and obinutuzumab + chlorambucil participants was 28.5 months (range: 1.7 to 40.3 months), 28.4 months (range: 0.1 to 40.8 months), and 28.0 months (range: 0.0 to 40.4 months), respectively. Acalabrutinib + obinutuzumab demonstrated a statistically significant improvement in IRC-assessed PFS compared with obinutuzumab + chlorambucil, with a 90% reduction in risk of disease progression or death (HR = 0.10 [95% CI: 0.06, 0.17]; $p < 0.0001$). Acalabrutinib monotherapy also demonstrated a statistically significant improvement in IRC-assessed PFS compared with obinutuzumab + chlorambucil, with an 80% reduction in risk of disease progression or death (HR = 0.20 [95% CI: 0.13, 0.30]; $p < 0.0001$). The median estimated PFS was not reached for acalabrutinib + obinutuzumab or acalabrutinib monotherapy and was 22.6 months (95% CI: 20.2, 27.6) for obinutuzumab + chlorambucil. The KM estimated 24-month PFS rate for acalabrutinib + obinutuzumab was 92.7% (95% CI: 87.4, 95.8), acalabrutinib monotherapy was 87.3% (95% CI: 80.9, 91.7), and obinutuzumab + chlorambucil was 46.7% (95% CI: 38.5, 54.6).

The key sensitivity analysis of PFS without censoring for subsequent anticancer therapy was consistent with the primary analysis and showed similar improvement in PFS for acalabrutinib + obinutuzumab and acalabrutinib monotherapy compared with obinutuzumab + chlorambucil (HR = 0.11 [95% CI: 0.06, 0.18] and HR = 0.20 [95% CI: 0.13, 0.31], respectively). All other sensitivity analyses were also consistent with the primary analysis. The clinical benefit with acalabrutinib was further demonstrated by a significant prolongation of TTNT compared with obinutuzumab + chlorambucil for both acalabrutinib + obinutuzumab (HR = 0.14 [95% CI: 0.08, 0.26]; $p < 0.0001$) and acalabrutinib monotherapy (HR = 0.24 [95% CI: 0.15, 0.40]; $p < 0.0001$). IRC-assessed ORR for acalabrutinib + obinutuzumab and obinutuzumab + chlorambucil was 93.9% (95% CI: 89.3, 96.5) and 78.5% (95% CI: 71.9, 83.9), respectively, with a statistically significant difference between treatment arms of 15.3%, $p < 0.0001$. The IRC-assessed ORR in the acalabrutinib monotherapy arm was 85.5% (95% CI: 79.6, 89.9) ($p = 0.0763$ compared with the obinutuzumab + chlorambucil arm).

The efficacy of acalabrutinib in patients with CLL has also been confirmed in number of supportive studies.

Efficacy data through 20 February 2020 are available on 124 participants with R/R MCL who were treated with acalabrutinib monotherapy (Study ACE-LY-004). With a median follow-up of 38.1 months, the ORR was 80.6%, with CR in 48% of participants.

Preliminary efficacy data through 03 August 2018 are available for 18 treatment-naïve participants and 20 R/R participants with MCL who received acalabrutinib administered concomitantly with BR (Study ACE-LY-106 [Part 1]). With a median follow-up of 20.6 months and 16.9 months for the 2 cohorts respectively, the ORR was 94.4% for the treatment-naïve cohort and 85.0% for the R/R cohort. A best response of CR was achieved in 72.2% and 65.0% of treatment-naïve and R/R participants, respectively.

Evidence for the efficacy of acalabrutinib monotherapy in relapsed or refractory DLBCL was assessed in 21 participants in Study ACE-LY-002. At the DCO of the final study report (30 October 2017), the ORR in this study was 23.8%. A total of 4 participants, including 2 in each cohort, achieved a CR, and one participant in the relapsed cohort had a PR as the best response.

Evidence for the efficacy of acalabrutinib monotherapy in participants with WM has been assessed in 106 participants in Study ACE-WM-001. At the DCO of the final study report (31 March 2021), the ORR was 93.4% under both the modified IWWM-3 and the IWWM-6 response criteria. In total, 2 participants under the modified IWWM-3 criteria, and 4 participants under the modified IWWM-6 criteria had a best response of CR.

A detailed description of the chemistry, pharmacology, efficacy, and safety of acalabrutinib is provided in the current IB.

1.2 Rationale for Study Design, Doses, and Control Groups

Chemoimmunotherapy is considered standard of care for previously untreated participants with CLL who have no significant comorbidities; however, chemoimmunotherapy is associated with significant toxicities. Furthermore, chemoimmunotherapy is not recommended in participants with del(17p) or TP53 mutation because of inferior response and outcome (Tam et al. 2008). In this population, available options are limited and include obinutuzumab or ibrutinib. Acalabrutinib has shown significant efficacy and tolerability in participants with TN or R/R CLL, and is currently being studied in randomized Phase III studies comparing it with standard of care treatments (Studies ACE-CL-006, ACE-CL-007, and ACE-CL-309). Studies ACE-CL-007 and ACE-CL-309 have met their primary endpoint and achieved superiority both in TN and R/R CLL against standard of care. Additional safety data are needed to further characterize less common associated AEs and management of common AEs. Data collected in a setting more reflective of real-world practice may further support participant management.

Dose selection for acalabrutinib was based on results in Study ACE-CL-001, a dose-escalation study in participants with CLL/SLL to determine a maximum tolerated dose. During Phase I of the study, no dose-limiting toxicities occurred in the qd dosing cohorts of 100 mg qd, 175 mg qd, 250 mg qd, and 400 mg qd. Furthermore, a well-tolerated dose and regimen of acalabrutinib at 100 mg bid provided near complete BTK occupancy over 24 hours at steady-state, with minimal inter-participant variability. The 100 mg bid regimen is the regulatory-approved dosage of acalabrutinib. See the IB for details.

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.

1.3 Benefit/Risk and Ethical Assessment

Acalabrutinib is an approved drug for the treatment of adult patients with CLL, in both the treatment-naïve and R/R setting, and the overall benefit-risk remains favorable.

Acalabrutinib is a highly selective, potent, orally administered covalent inhibitor of BTK. In the Phase I/II study of acalabrutinib in participants with CLL, no dose-limiting toxicities were identified at any evaluated dose levels, which included dosages up to 400 mg qd or 100 to 200 mg bid. The ORR in the evaluable participants (n = 60) for this study was 95% (Byrd et al. 2016a) with a median follow-up of 14.3 months.

Precautionary safety measures and regular monitoring of safety by a sponsor-appointed safety committee will also enable early identification of safety signals in the study and minimize the

risk to participants. See Section 1.5 for information regarding the Safety Monitoring Committee.

More detailed information about the known and expected benefits and potential risks of acalabrutinib may be found in the IB and DSURs.

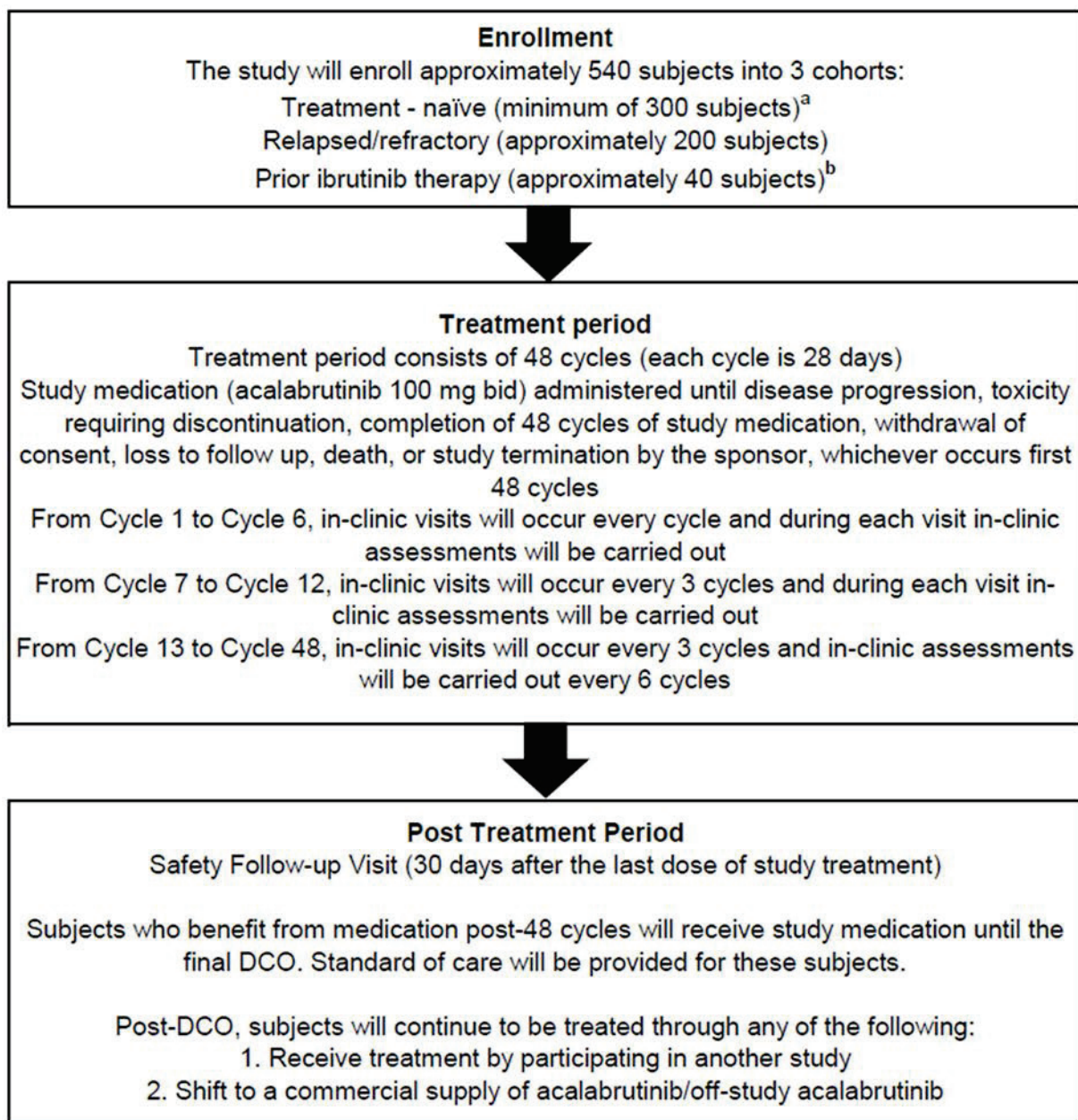
1.4 Study Design

This global, Phase IIIb, multicenter, open-label, single-arm study will evaluate the safety and efficacy of acalabrutinib 100 mg bid in approximately 540 participants with CLL. Participants will be enrolled into one of the 3 following cohorts:

- Treatment-naïve 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 G](#)) and/or have a creatinine clearance of 30 to 69 mL/min using the Cockcroft-Gault equation. This cohort will not be enrolled in the UK.
- Relapsed/refractory cohort: participants who have received prior 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. This cohort will not be enrolled in the US.

The general study design is summarized in [Figure 1](#).

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.

^a 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.

^b 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.

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. Adverse events that lead to discontinuation of study intervention will also be assessed.

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

Participants will remain on study intervention until completion of 48 cycles (28 days per cycle) or until study drug 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 regulation. Details are provided in Section 4.3.

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 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).

1.5 Study Governance and Oversight

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. Final analyses for this study will be performed after all participants complete 48 cycles of study intervention (or discontinued before) including 30 days of follow-up after the last dose of study intervention. Additionally, this study will be monitored on an ongoing basis. Additional safety reviews may be added based on recommendation by the DSMC, based on the first safety analysis review realized after full study enrollment (Section 8.5.7).

Data collected regarding COVID-19 will be analyzed and results presented in the CSR.

2 STUDY OBJECTIVES

2.1 Primary Objective

Primary objective	Endpoints
To evaluate the safety and tolerability of acalabrutinib monotherapy in participants with treatment-naïve or relapsed/refractory chronic lymphocytic leukemia	- Frequency, severity, and relatedness of all AEs, which will also include: - Grade ≥ 3 adverse events - Serious adverse events - Events of clinical interest 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 as defined in Section 6.4 - Adverse events of special interest defined as ventricular arrhythmias - Adverse events that lead to discontinuation of treatment

2.2 Secondary Objective

Secondary objective	Endpoints
To evaluate the investigator-assessed overall response, duration of response, and progression-free survival in participants receiving acalabrutinib monotherapy	Overall response Duration of response Progression-free survival

2.3 Exploratory Objectives

Exploratory objectives	Endpoints
To evaluate patient-reported symptoms and health-related quality of life following treatment with acalabrutinib monotherapy	European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 Patient-reported Outcomes version of the Common Terminology Criteria for Adverse Events
To characterize the pharmacokinetics of acalabrutinib and its metabolite (ACP-5862)	Summarized plasma concentrations of acalabrutinib and ACP-5862 at specified time points Pharmacokinetic parameters by population analyses as appropriate

3 PARTICIPANT SELECTION, ENROLLMENT, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each participant should meet all inclusion criteria and none of the exclusion criteria to be enrolled. Under no circumstances can there be exceptions to this rule. Participants who do not meet the entry requirements will be screen failures (see Section 3.10.1).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

3.1 Inclusion Criteria

For inclusion in the study, participants should fulfill the following criteria:

- Men and women ≥ 18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place)
- Diagnosis of CLL that meets all published diagnostic criteria (Hallek et al. 2018) as stated below:
 - 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
 - Prolymphocytes may comprise $< 55\%$ of blood lymphocytes during screening
 - Presence of $\geq 5 \times 10^9$ B lymphocytes/L (5000/ μ L) in the peripheral blood (at any point since the initial diagnosis)

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/ μ L)
 - b. Massive (ie, ≥ 6 cm below the left costal margin), progressive, or symptomatic splenomegaly
 - c. Massive nodes (ie, ≥ 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 LDT of < 6 months. Lymphocyte doubling time 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 < $30 \times 10^9/L$ (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 (eg, 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 (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

4. Must meet one 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 (see [Appendix G](#))
 - 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.
5. Eastern Cooperative Oncology Group performance status of ≤ 2 .
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 intervention. Contraception measures and restrictions on sperm donation are not required for male participants. See [Appendix F](#) for guidance and definitions for reproduction and contraception.
7. Fluorescence in situ hybridization for which the NGS method is preferred within 60 days during screening up to before the first dose reflecting the presence or absence of del(17p), del(13q), del(11q), 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.
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.

3.2 Exclusion Criteria

Participants should not enter the study if any of the following exclusion criteria are fulfilled:

1. Participants who have had disease progression while on a BTKi for any malignant or non-malignant condition
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
3. History of confirmed progressive multifocal leukoencephalopathy
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 NYHA Functional Classification, or 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, except in Finland and the Republic of South Korea, where this is applicable to all 3 cohorts; also, the prior ibrutinib therapy cohort will not be enrolled in the US).
5. Malabsorption syndrome, disease significantly affecting GI 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
6. Evidence of active Richter's transformation. If Richter's transformation is suspected (ie, LDH increased, asymmetric fast LN growth or clinical suspicion), it should be ruled out with positron emission tomography-computed tomography (PET-CT) and/or biopsy according to guidelines
7. Central nervous system involvement by CLL
8. Known history of human immunodeficiency virus, serologic status reflecting active HBV or HCV 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 intervention
 - a. Participants who are anti-HBc positive and who are anti-HBs negative will need to have a negative hepatitis B virus PCR result before enrollment. Those who are HBsAg positive or hepatitis B virus PCR positive will be excluded.
 - b. Participants who are HCV antibody positive will need to have a negative HCV PCR result before enrollment. Those who are HCV PCR positive will be excluded.

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).
10. History of stroke or intracranial hemorrhage within 6 months before the first dose of study intervention.
11. History of bleeding diathesis (eg, hemophilia or von Willebrand disease).
12. Presence of a GI ulcer diagnosed by endoscopy within 3 months before screening.
13. Major surgical procedure within 4 weeks before first dose of study intervention.
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 intervention.
14. Requires treatment with proton-pump inhibitors (eg, 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.
15. All participants requiring or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) within 7 days before first dose of study intervention. 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.
16. Absolute neutrophil count < $0.50 \times 10^9/\text{L}$ or platelet count < $30 \times 10^9/\text{L}$, unless proven due to CLL and raised above the limits by granulocyte colony-stimulating factor therapy and/or pooled platelet transfusion.
17. Total bilirubin > $3.0 \times \text{ULN}$; or AST or ALT > $3.0 \times \text{ULN}$. 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 TBL number. The investigator must also document that hemolysis has been ruled out along with (near)-normal LDH and haptoglobin.
18. Estimated creatinine clearance of < 30 mL/min, calculated using the formula of Cockcroft and Gault or by direct assessment (ie, creatinine clearance or EDTA clearance measurement).
19. Breastfeeding or pregnant
20. Received any chemotherapy, external beam radiation, investigational drug, or any other anti-CLL therapy within 30 days before first dose of study intervention.
21. Concurrent participation in another therapeutic clinical study.
22. History of or ongoing interstitial lung disease.

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 intervention is prohibited.

Procedures for withdrawal of incorrectly enrolled participants see Section 3.4.

3.3 Participant Enrollment

Investigators should keep a participant screening log of all participants who entered pre-study screening.

The investigator will:

- Obtain signed ICF from the potential participant or guardian/legal representative (if allowed per local regulations) before any study specific procedures are performed.
- Assign each potential participant a unique enrollment number.
- Determine participant eligibility (see Section 3.1 and Section 3.2).
- Complete and provide the Pre-enrollment Form as supporting documentation for eligibility review performed by study medical monitor(s) (for prior ibrutinib therapy cohort ONLY, which will not be enrolled in the US).

If a participant withdraws from participation in the study, then the enrollment number cannot be reused.

3.4 Procedures for Handling Incorrectly Enrolled Participants

Participants who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study intervention. There can be no exceptions to this rule eg, no waiver for inclusion can be granted. The sponsor's study physician must ensure all decisions are appropriately documented.

3.5 Methods for Assigning Treatment Groups

This is an open-label single-arm study.

3.5.1 Methods for Ensuring Blinding

Blinding measures are not applicable as this is an open-label study.

3.6 Methods for Unblinding

Unblinding measures are not applicable as this is an open-label study.

3.7 Restrictions

None other than those listed in the inclusion and exclusion criteria.

3.8 Drug-drug Interactions

Acalabrutinib is predominantly metabolized by CYP3A enzymes and hence can be subject to drug-drug interactions. Acalabrutinib is not a clinically relevant inhibitor or inducer of CYP3A enzymes, therefore is not expected to drive drug-drug interactions through this pathway.

As acalabrutinib is metabolized by CYP3A, participants should be strongly cautioned against using herbal remedies or dietary supplements (in particular, St John's wort, which is a potent CYP3A inducer).

In vitro data indicate that acalabrutinib is a P-glycoprotein and BCRP substrate.

Acalabrutinib may increase exposure to BCRP substrates by inhibition of intestinal BCRP and should be coadministered with caution with narrow therapeutic index BCRP substrates.

Recommendations regarding use of acalabrutinib with CYP3A inhibitors or inducers and gastric acid reducing agents are provided in [Table 1](#).

Table 1 Use with CYP3A Inhibitors or Inducers and Gastric Acid Reducing Agents

	Coadministered medicinal product	Recommended acalabrutinib use
CYP3A inhibitors	Strong CYP3A inhibitor	Avoid concomitant use. If these inhibitors will be used short-term (such as anti-infectives for up to 7 days), interrupt acalabrutinib.
	Moderate CYP3A inhibitor	Reduce dose to 100 mg once daily ^a .
	Mild CYP3A inhibitor	No dose adjustment.
CYP3A inducers	Strong CYP3A inducer	Avoid concomitant use. If a participant requires treatment with a strong CYP3A inducer, increase the acalabrutinib dose to 200 mg bid during concomitant administration with the strong inducer and return to recommended dose of 100 mg bid after stopping the strong CYP3A inducer.
Gastric acid reducing agents	Proton-pump inhibitors	Avoid concomitant use.
	H ₂ -receptor antagonists	Take acalabrutinib 2 hours before taking a H ₂ -receptor antagonist.
	Antacids	The interval between taking the medicinal products should be at least 2 hours.

^a Recommendation per USPI is 100 mg once daily.
bid = twice daily; CYP = cytochrome P450; USPI = United States Prescribing Information.

3.9 Dose Modification and Discontinuation of Study Intervention

3.9.1 Dose Modification

In case a dose reduction is necessary, the study intervention will be administered as follows:

Dose modification guidelines for study intervention-related toxicities are provided in [Table 2](#). Appropriate and optimal treatment of the toxicity is assumed prior to considering dose modifications. Prior to discontinuation of study intervention due to toxicities, please consult with the study physician.

Table 2 Dose Modifications for Study Intervention-related Toxicities

Adverse reaction	Adverse reaction occurrence	Dose modification (Starting dose = 100 mg approximately every 12 hours)
Grade 3 thrombocytopenia with bleeding, Grade 4 thrombocytopenia	First and second	Interrupt acalabrutinib. Once toxicity has resolved to Grade 1 or baseline, acalabrutinib may be resumed at 100 mg approximately every 12 hours.
Or Grade 4 neutropenia lasting longer than 7 days	Third	Interrupt acalabrutinib. Once toxicity has resolved to Grade 1 or baseline, acalabrutinib may be resumed at a reduced frequency of 100 mg once daily.
Grade 3 or greater non-hematological toxicities	Fourth	Discontinue acalabrutinib.

Any other clinically important event where dose delays may be considered appropriate by the investigator should be discussed with the medical monitor. Study intervention may be held for a maximum of 28 consecutive days from expected dose due to toxicity, study disruptions due to cases of civil crisis, natural disaster, or public health crisis. (For Germany, study intervention may be held for a maximum of 28 consecutive days from expected dose due to toxicity or study disruptions due to the COVID-19 pandemic only.) During this period, appropriate laboratory monitoring should be performed per institutional guidelines, to align as closely as possible with the protocol. Study intervention should be permanently discontinued in the event of study intervention being held or being unavailable for > 28 days, unless reviewed and approved by the medical monitor (including in the Disease Follow-up period following Cycle 48).

Note: temporary withholding of acalabrutinib for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. Transient worsening of disease during temporary interruption of study intervention (eg, for drug-related toxicity, surgery, or intercurrent illness) may not indicate disease progression. In such circumstances, and if medically appropriate, participants may resume study intervention and relevant clinical, laboratory, and/or radiologic assessments should be done to document whether tumor control can be maintained or whether actual disease progression has occurred.

If study intervention is reduced for apparent treatment-related toxicity, the dose need not be re-escalated, even if there is minimal or no toxicity with the reduced dose. However, if the participant tolerates a reduced dose of study intervention then the dose may be increased to the next higher dose level, at the discretion of the investigator. Such re-escalation may be particularly warranted if further evaluation reveals that the AE that led to the dose reduction was not treatment-related. Any changes to the dosing regimen must be recorded in the Dose Administration of Acalabrutinib page in the eCRF.

3.9.2 Discontinuation From Study Intervention

Note that discontinuation from study intervention is NOT the same as complete withdrawal from the study. If a participant discontinues study intervention and does not withdraw consent for study participation, a 30-day SFU visit will be conducted after the participant has received the last dose of study intervention.

The investigator, in consultation with the medical monitor, may withdraw any participant from study intervention, if, in the investigator's opinion, it is not in the participant's best interest to continue.

Participants may be withdrawn from study intervention for the following reasons:

- Disease progression
- Start of alternative anticancer therapy
- AE
- Development of unacceptable toxicity
- Pregnancy
- Investigator decision
- Withdrawal of consent. The participant is, at any time, free to discontinue his/her participation in the study, without prejudice
- Decision by sponsor to terminate the study
- Participant loss to follow-up
- Death
- Other

The investigator should instruct the participant to contact the site before or at the time if study intervention is stopped. A participant that decides to discontinue study intervention will always be asked about the reason(s) and the presence of any AEs. The date of last intake of study intervention should be documented in the eCRF. All study intervention should be returned by the participant at the next on-site study visit or unscheduled visit.

Participants who are removed from study intervention will not be replaced.

3.9.2.1 Temporary Discontinuation

Study intervention may be held for a maximum of 28 consecutive days from expected dose due to toxicity, study disruptions due to cases of civil crisis, natural disaster, or public health crisis. (For Germany, study intervention may be held for a maximum of 28 consecutive days from expected dose due to toxicity or study disruptions due to the COVID-19 pandemic only.) For more details regarding dose modification, see Section [3.9.1](#).

3.10 Withdrawal from Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If the participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the global study team.

Note that discontinuation from study intervention is NOT the same as complete withdrawal from the study.

A participant may withdraw from the study (eg, withdraw consent), at any time (study intervention and assessments) at his/her own request, without prejudice to further treatment.

When a participant withdraws before completing the study, the reason for withdrawal must be documented in the eCRF and in the source documents. See [Table 3](#) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. All study intervention should be returned by the participant. Participants who withdraw consent should still be encouraged to complete the study follow-up assessments

before withdrawing consent, but these assessments cannot be mandated once consent is withdrawn.

Participants who are withdrawn will not be replaced.

3.10.1 Screen Failures

Screen failures are defined as participants who signed the ICF to participate in the clinical study but are not enrolled. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Participants who fail screening based on no immediate requirement for treatment can be rescreened in the future when they are in need of treatment for CLL on a case-by-case basis as determined by the medical monitor. For example, potential participants who fail screening because of recent infection (participants with infections requiring IV treatment [Grade 3 or 4] within the last 4 weeks prior to enrollment) may be rescreened once their infections resolve. For information on additional rescreening for screen failure due to study disruption due to the COVID-19 pandemic refer to [Appendix M](#).

3.10.2 Study Early Termination

The sponsor retains the right to terminate the study and remove all study materials from a study site at any time. Specific circumstances that may precipitate such termination are:

- Unsatisfactory participant enrollment regarding quality or quantity.
- Significant or numerous deviations from study protocol requirements, such as failures to perform required evaluations on participants and maintain adequate study records.
- Inaccurate, incomplete and/or late data recording on a recurrent basis.
- The incidence and/or severity of AEs in this or other studies indicating a potential health hazard caused by the study intervention.

3.10.3 Loss to Follow-up

A participant will be considered potentially lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant or next of kin by, eg, repeat telephone calls, certified letter to the participant's last known mailing address or local equivalent methods per local regulations. A minimum of 5 contact attempts should be made. These contact attempts should be documented in the participant's medical record.
- Efforts to reach the participant should continue for 60 days from the last missed visit. Should the participant be unreachable at the end of 60 days, the participant should be considered to be lost to follow-up with unknown vital status at end of study and censored at the latest follow-up contact.

4 STUDY PLAN AND TIMING OF PROCEDURES

Study procedures and their timing are summarized in the SoA (see [Table 3](#)). The purpose of obtaining these detailed measurements is to ensure adequate safety and efficacy assessments. Clinical evaluations and laboratory assessments may be repeated more frequently if clinically indicated. This study will use local laboratory testing for safety laboratory evaluations.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

Missed evaluations should be rescheduled and performed as close to the original scheduled date as possible. An exception can be made when rescheduling becomes, in the investigator's opinion, medically unnecessary or unsafe because it is too close in time to the next scheduled evaluation. In that case, the missed evaluation should be abandoned.

Table 3 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	-	-
CT/MRI scan ^l	X	-	-	-	X (1 year after initial dose of study intervention)	-		-
BM biopsy and aspirate ^m	-	-	-	-	X (1 year after	-		-

Table 3 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	
					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	-	-					-
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	-	-			-	-	-

Table 3 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	
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	-	-	-
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. 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 prolymphocytes 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.

4.1 Screening/Enrollment Period

All screening assessments shown in the SoA (see [Table 3](#)) will be performed a maximum of 28 days before starting study intervention.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

(For the Republic of South Korea, hematology, serum chemistry, and creatinine clearance must be performed within 7 days of C1D1. All other tests will be performed within the screening window of 28 days.)

4.1.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

Note: For Germany, this guidance only applies to the COVID-19 pandemic. In case of further events requiring mitigation of study procedures, these will be addressed separately at the time of their occurrence.

The guidance given below and in [Appendix M](#), while taking into account any other regional or local regulations and/or guidance, supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study participants become infected with severe acute respiratory syndrome coronavirus 2 or similar pandemic infection), which would prevent the conduct of study-related activities at study sites, thereby compromising the study-site staff or the participant's ability to conduct the study. The investigator or designee should contact the study sponsor to discuss whether the mitigation plan below on rescreening should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study participants, maintain compliance with GCP, and minimize risks to study integrity.

In cases where participants test COVID-19-positive, the investigator will assess the benefits/risks for study intervention intake versus COVID-19 treatment, and the participant will continue study intervention at the investigator's discretion. The participant will have tests for serum immunoglobulin levels after 2 months of COVID-19 infection cure.

Participants should be vaccinated if it is determined by the investigator to be in their best interest. There is no known contraindication for any of the participants on acalabrutinib studies. Participants should still protect themselves from exposure to COVID-19 after vaccination.

Should the participant have AEs after immunization, the investigator is encouraged to share relevant information with the sponsor.

For all applicable countries following EU regional guidance on the management of COVID-19 in clinical studies, refer to [Appendix M, EMA 2022](#) (eg, changes of monitoring, including remote source data verification and protocol deviations), and [BfArM 2022](#) for further guidance.

Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

- Obtaining reconsent for the mitigation procedures (note, in the case of verbal reconsent, the ICF should be signed at the participant's next contact with the study site).
- Rescreening: additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened participants. The investigator should confirm this with the designated study physician.
- Home or remote visit: performed by a site qualified HCP or HCP provided by a TPV.
- Telemedicine visit: remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

For further details regarding study conduct during civil crisis, natural disaster, or public health crisis, refer to [Appendix M](#).

4.2 Treatment Period (up to 48 Cycles)

The treatment period will extend from the start of enrollment until study intervention discontinuation. Each treatment period consists of 48 cycles. Each cycle will consist of 28 days (4 weeks). Participants will receive study intervention (acalabrutinib, 100 mg bid) for up to 48 cycles. A cycle is considered only when participant received the study medication during a scheduled visit. During the treatment period in each cycle (28 days) no interruptions are permitted unless specified in the protocol Section [3.9.2.1](#).

From Cycle 1 to Cycle 6, in-clinic visits will occur every cycle and during each visit in-clinic assessments will be carried out. From Cycle 7 to Cycle 12, in-clinic visits will occur every 3 cycles and during each visit in-clinic assessments will be carried out. From Cycle 13 to Cycle 48, in-clinic visits will occur every 3 cycles and in-clinic assessments will be carried out every 6 cycles. An unscheduled visit (no IP dispensed) may be conducted if required at the investigator's discretion.

At cycles with no on-site visits, concomitant medication and AEs will be recorded via a telephone call. 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.

4.3 Post-treatment Period

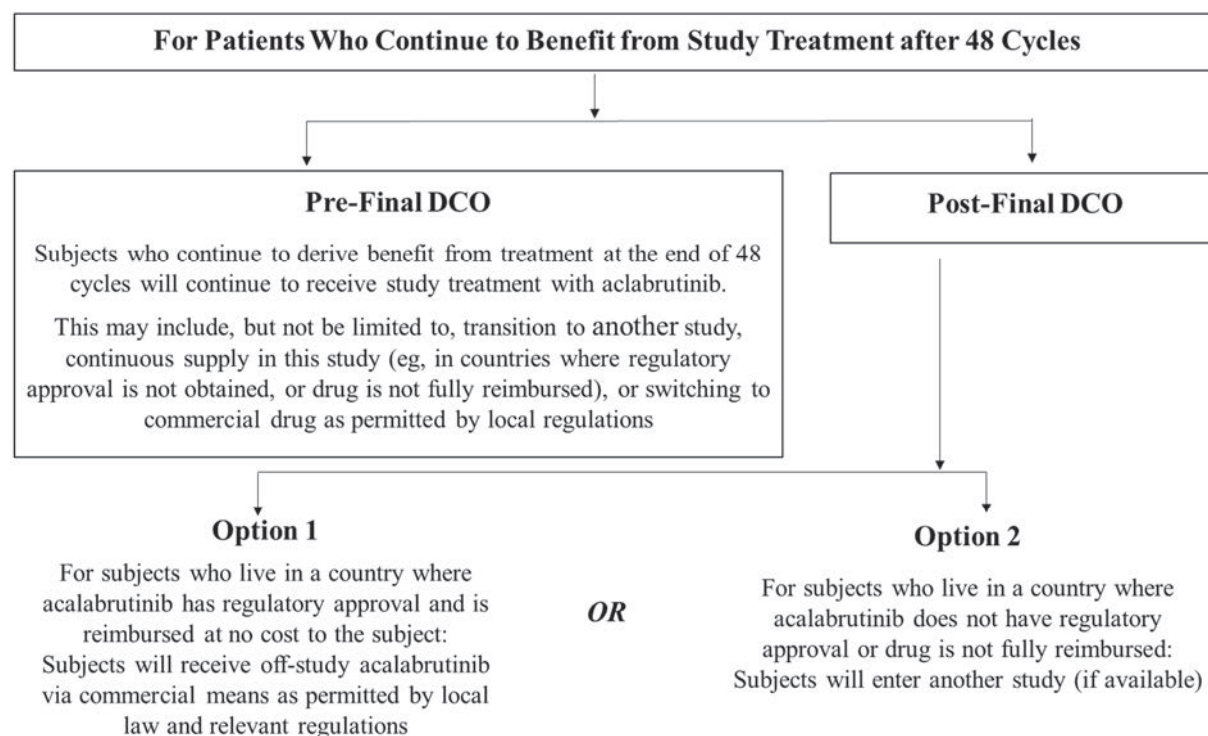
All participants will have a SFU visit no less than 30 days after the last dose of study intervention. A participant who experiences disease progression while on study intervention will need to complete the SFU visit just before shifting to new medication, or no less than 30 days, whichever occurs first.

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 followed in the Disease Follow-up period q24w until discontinuation of study intervention due to, for example, disease progression or toxicity, transition to another study or to a regulatory-approved off-study acalabrutinib, withdrawal of consent, loss to follow-up, death, or study termination by the sponsor.

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.

[Figure 2](#) presents the options for participants who complete the study.

Figure 2 Post-study Options



Note: See the SoA (Table 3) 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.

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 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.

Final analysis for this study will be performed after all participants complete 48 cycles (or discontinued before), including 30 days of SFU.

Participants who are being monitored for hepatitis reactivation with hepatitis B virus PCR testing are recommended to have quantitative PCR testing q12w or per institutional guidelines for 1 year after coming off study intervention.

5 STUDY ASSESSMENTS

Study procedures and their timing are summarized in the SoA (see [Table 3](#)).

Authorized study-site personnel will complete eCRFs designed for this study according to the completion guidelines that will be provided within the clinical database. The investigator will ensure that the eCRFs are accurate, complete, legible, and completed promptly. The investigator will sign the completed eCRFs, and a copy will be archived at the study site.

The principal investigator will ensure that all biological samples are labeled and shipped in accordance with the laboratory manual and the International Airline Transportation Association Guidance Document (see [Appendix B](#)).

5.1 Efficacy Assessments

5.1.1 Response

Response evaluation will be done at least 1 year after initial dose of study intervention and per institutional guidelines. An unscheduled visit may be conducted if required as determined by the site. If additional response assessments are performed per institutional guidelines outside of the 1-year assessment, these must be recorded in the eCRF.

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 whether 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).

Response will be classified as CR, CRi (ie, persistent anemia, thrombocytopenia, or neutropenia), PR, SD, or PD (see [Section 6.5.7](#)).

5.1.2 Survival

Each participant should be followed until one of the following occurs: completion of 48 cycles, study intervention discontinuation (eg, disease progression, toxicity), withdrawal of consent, loss to follow-up, death, or study termination by the sponsor, whichever occurs first. Also, participants who complete 48 cycles and continue to receive treatment post-48 cycles will be followed in the same manner up until study intervention discontinuation (eg, disease progression, toxicity), withdrawal of consent, loss to follow-up, death, or study termination by the sponsor, whichever occurs first.

5.1.3 Patient-reported Outcomes

Patient-reported outcomes, an umbrella term referring to all outcomes and symptoms, are directly reported by the participant. PROs have become a significant endpoint when evaluating effectiveness of treatments in clinical studies. The following PROs will be administered in the study through a web-based ePRO data capture system according to availability of certified translation: EORTC-QLQ-C30 and PRO-CTCAE at time points indicated in the SoA (see [Table 3](#)).

5.1.3.1 European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30

The EORTC-QLQ-C30 was developed by the EORTC Quality-of-Life Group 1993. It consists of 30 items and measures cancer participants' functioning (health-related quality of life) and symptoms ([Aronson et al. 1993](#)) for all cancer types. Questions can be grouped into 5 multi-item functional scales (physical, role, emotional, cognitive, and social); 3 multi-item symptom scales (fatigue, pain, and nausea and vomiting); a 2-item global health-related quality of life scale; 5 single items assessing additional symptoms commonly reported by cancer participants (dyspnea, loss of appetite, insomnia, constipation, diarrhea) and 1 item on the financial impact of the disease. The EORTC-QLQ-C30 is a valid and reliable PRO instrument in this participant population and found in [Appendix J](#).

5.1.3.2 Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events

The PRO-CTCAE system was developed by the NCI. The PRO-CTCAE will only be administered in those countries or regions where a linguistically-validated version exists. The PRO version of the CTCAE is an item-bank of symptoms experienced by participants while undergoing treatment of their cancer. It was developed by recognizing that collecting symptom data directly from participants using PRO tools can improve the accuracy and efficiency of symptomatic AE data collection. This was based on findings from multiple studies demonstrating that physicians and nurses underestimate symptom onset, frequency, and severity in comparison with participant ratings ([Basch et al. 2009](#), [Litwin et al. 1988](#), [Sprangers and Aronson 1992](#)). The PRO-CTCAE instrument is found in [Appendix K](#).

To date, 81 symptoms of the CTCAE v5.0 have been identified to be amenable to participant reporting. These symptoms have been converted to participant terms (eg, CTCAE term “myalgia” converted to “aching muscles”). 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.

The items included in the PRO-CTCAE have undergone extensive qualitative review among experts and participants. Using cognitive testing methods, these items and the additional

questions for some of the symptoms have been extensively evaluated by cancer participants, so that symptoms of interest are clear, comprehensible, and measurable.

Not all items are administered in any one clinical study. The intention is to only ask participants to complete those items that are considered relevant for the study, site of the cancer, and cancer treatment. For this study, the following items are considered relevant and will be assessed: headache, diarrhea, fatigue, nausea, vomiting, abdominal pain, rash, muscle pain, nosebleed, heart palpitations, bruising, joint pain, and constipation.

5.1.3.3 Administration of Patient-reported Outcomes Questionnaires

Participants will complete PRO assessments at home, and sometimes at the investigational site, using an electronic capture system (internet-based). Participants will be trained on how to enter their data into the internet-based platform.

PRO questionnaires completed at site visits must be completed first prior to treatment administration and ideally before any discussions of health status to avoid biasing the participant's responses to the questions. As feasible, site staff should also ensure PRO questionnaires are completed prior to other study procedures, such as collection of laboratory samples, to avoid bias.

Each site must allocate the responsibility for the administration of the ePROs to a specific individual (eg, a research nurse or study coordinator) and, if possible, assign a backup person to cover if that individual is absent.

The investigator will arrange for relevant training for the set-up of the internet-based PRO data collection and training participants in how to self-administer the ePROs using the internet. Participants should complete the ePROs in accordance with the SoA (see [Table 3](#)). The ePROs will be completed until the end of Cycle 48. The significance and relevance of the PRO data should be explained carefully to participants so that they are motivated to comply with the data collection. Reminders should be sent to participants at home, as needed to ensure compliance with the assessment schedule.

The following guidelines should be followed:

- When both instruments are due to be completed, EORTC-QLQ-C30 should be assessed before PRO-CTCAE (and the internet-based PRO should be programmed accordingly).
- Electronic PRO completion should be done by the participant in private. When assessments occur on site, site staff should ensure that each participant gets a quiet place to do the assessments.
- The research nurse or appointed site staff must explain to participants the value and relevance of study participation and inform them that these questions are being asked to find out, directly from them, how they feel. The research nurse or appointed site staff should also stress that the information is not routinely shared with the study staff. Therefore, if the

participants have any medical problems, they should discuss them with the doctor or research nurse separately from the ePRO assessment.

- The research nurse or appointed site staff must train the participant on how to enter the PRO data, using the materials and training provided by the ePRO vendor, and provide guidance on whom to call if there are problems with the data entry when the participant is completing the ePROs at home.
- The research nurse or appointed site staff should remind participants that there are no right or wrong answers.
- The research nurse or appointed site staff must avoid clarifying items to avoid bias.
- The participant must not receive help from relatives, friends, or clinic staff to respond to the ePROs. If a participant uses visual aids (eg, spectacles or contact lenses) for reading and does not have them when attending the clinic, the participant should be asked to complete the ePROs at home instead, if it is within the time window. Site staff must not read or complete the ePROs on behalf of the participant.
- If the participant is unable to read (eg, blind or illiterate), that participant is exempted from completing the ePROs and may still participate in the study. Participants exempted in this regard should be flagged appropriately by the site staff.

The research nurse or appointed site staff must monitor compliance to ensure all data are captured. Compliance must be checked at each study visit to identify problems early. The participant will be flagged in the routine compliance report generated by the ePRO system. If the site receives an email notification regarding the participant's compliance, a check-in call from the site to ask the participant if he/she has any difficulties is highly recommended.

5.2 Safety Assessments

5.2.1 Adverse Events

The reporting of AEs is described in [Section 6](#).

5.2.2 Laboratory Safety Assessments

All protocol-required laboratory assessments must be conducted as defined in the SoA (see [Table 3](#)). Some laboratory assessments will be done at local laboratories or central laboratories if required and requested by sites. FISH, TP53 mutation sequencing, IGHV, and karyotyping will be done at local or central laboratory.

The date, time of collection, and results (local values, units, and reference ranges) will be recorded on the appropriate eCRF.

Hematology assessments must include complete blood count with differential, including, but not limited to WBC count, hemoglobin, hematocrit, platelet count, ANC, and ALC. Cycle 1, Day 1 hematology does not need to be repeated if screening hematology was done within 5 days.

Whole blood samples will be analyzed for absolute T/B/NK counts (CD3+, CD19+, CD4+, CD8+, CD16+/56+ are mandatory, CD20, CD23, CD5, and prolymphocytes as optional using a standard cell marker panel). This assay will be performed on the same blood sample collected for standard hematology.

Serum chemistry must include albumin, ALP, ALT, AST, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, creatine kinase, glucose, LDH, magnesium, phosphate/phosphorus, potassium, sodium, TBL, total protein, and uric acid. Creatinine clearance will be assessed per the SoA. 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. Serum samples will also be analyzed for quantitative immunoglobulin (IgG, IgM, IgA) levels and serum β 2-microglobulin. Cycle 1 Day 1 serum chemistry does not need to be repeated if screening serum chemistry was done within 5 days.

Additional safety samples may be collected if clinically indicated at the discretion of the investigator. The date, time of collection, and results (values and units) will be recorded on the appropriate eCRF.

The investigator should assess the available results regarding clinically relevant abnormalities. Abnormal laboratory parameters that are clinically significant will be reported as an AE (see [Table 5](#)). See [Appendix D](#) for actions required in cases of increases in liver biochemistry and evaluation of Hy's Law.

5.2.3 Electrocardiograms

Electrocardiograms will be performed at screening and at the SFU visit. 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 a supine position and resting for at least 10 minutes before any study-related ECGs. Heart rate, PR interval, 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 to study intervention will be reported as an AE (see [Table 5](#)).

5.2.4 Vital Signs

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 will be reported as an AE (see [Table 5](#)).

5.2.5 Pregnancy Testing

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. The timing of pregnancy tests is indicated in the SoA (see [Table 3](#)). See [Appendix F](#) for guidance and definitions for reproduction and contraception.

An additional pregnancy test should also be performed at the time point when highly effective contraception is no longer required per protocol, or as determined necessary by the investigator or required by local health authority regulations to establish the absence of pregnancy at any time during a participant's participation in this study.

5.2.6 Concomitant Medications

Concomitant medications will be recorded from screening through 30 days after the last dose of study intervention as defined in the SoA (see [Table 3](#)). At cycles with no on-site visits, concomitant medication will be recorded via a telephone call.

5.3 Other Assessments

All protocol-required assessments must be conducted as defined in the SoA (see [Table 3](#)).

5.3.1 Medical History and Prior Medications

Complete medical history from the date of CLL diagnosis, will include concurrent medical signs and symptoms, alcohol use and, if a smoker, a description of use (cigar, cigarette, etc.; cigarettes in pack/year). History of substance abuse 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 at screening in the eCRF.

5.3.2 Eastern Cooperative Oncology Group

The ECOG will be assessed according to [Table 4](#).

Table 4 Eastern Cooperative Oncology Group Performance Status

Grade	Eastern Cooperative Oncology Group
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: [Oken et al. 1982](#)

5.3.3 Cumulative Illness Rating Scale

Cumulative Illness Rating Scale is an indicator of illness severity and comorbidity in older participants ([Extermann et al. 1998](#)) (see [Appendix G](#)). Cumulative Illness Rating Scale scoring is to be performed by a licensed provider (eg, physician, physician's assistant, or nurse).

Note: This assessment does not apply to participants in the UK, as participants will not be enrolled into the TN cohort of this study.

5.3.4 Disease-related Symptoms

Disease-related symptoms will be assessed and recorded in the participant records and are defined per [Hallek et al. 2018](#) as:

- Unintentional weight loss of 10% or more within the previous 6 months.
- Significant fatigue (ie, ECOG performance status ≥ 2 ; inability to work or perform usual activities).
- Fevers higher than 100.5°F or 38°C for 2 or more weeks without other evidence of infection.
- Night sweats for more than 1 month without evidence of infection.

5.3.5 Physical Examination

Physical examination will include height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal, nervous, lymphatic system and general appearance. The lymphatic system examination will include bidimensional measurements of palpable LNs and measurement of spleen and liver sizes 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 (see [Table 3](#)).

5.3.6 Radiologic Imaging

At screening and 1 year after initial dose of study intervention, 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 IV CT contrast agents will have CT scans performed with oral contrast. Magnetic resonance imaging may be used for imaging assessments if a contrast CT scan is contraindicated or unobtainable. Any additional imaging will be performed according to institutional standards.

5.3.7 Bone Marrow Aspirate and Biopsy

Bone Marrow aspirate and biopsy to confirm a CR must be done within 4 weeks of the CT/MRI scan that showed suspected CR. If BM aspirate and biopsy was performed to confirm CR within the prior 90 days, then no additional biopsy or aspirate is necessary.

5.3.8 Hepatitis Serology and PCR

Hepatitis serology will include HBsAg, anti-HBs, anti-HBc, and anti-HCV.

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 every 12 weeks (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 HBV. Because IVIG may cause false-positive hepatitis serology, PCR testing every 12 weeks 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 HCV or who are anti-HCV 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.

5.3.9 Fluorescence in situ Hybridization and Karyotyping

Fluorescence in situ hybridization (for which the NGS method is preferred) within 60 days during screening up to before the first dose, reflecting the presence or absence of del(17p), del(13q), del(11q), 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.

5.3.10 Pharmacokinetic Assessments

Sparse PK samples will be collected from all participants to investigate the PK of acalabrutinib and its metabolite, ACP-5862. Blood samples for PK analysis of acalabrutinib and ACP-5862 will be collected on Day 1 of Cycle 3 and Day 1 of Cycle 15. Samples will be collected 30 to 60 minutes before dosing and at 1 hour ($\pm$ 15 minutes) after dosing.

On the day of sampling, the participant will not take a dose of any study intervention before arrival at the clinic. The study intervention administration will be observed by the clinic staff. The actual time of the observed dose and the blood draws for PK samples must be accurately recorded to the minute in the eCRF.

At each PK time point, one 4-mL lithium heparin tube should be collected for acalabrutinib and ACP-5862 PK and processed and shipped per the instructions in the laboratory manual. The bioanalytical laboratory will analyze the samples using validated methods. Full details of the analytical method will be described in a separate bioanalytical report.

Residual PK samples may be used for exploratory biomarker development and/or exploratory analysis of acalabrutinib-related metabolites and/or of concomitant medications. In addition, PK samples may be disposed of or destroyed and anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR. Pharmacokinetic samples will be disposed of after finalization of the CSR unless requested to be stored for future analyses.

Instructions for the collection and handling of biological samples will be provided in the study specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples see [Appendix C](#).

- Pharmacokinetic samples will be disposed of after the bioanalytical report finalization or 6 months after issuance of the draft bioanalytical report (whichever is earlier), unless consented for future analyses.
 - Pharmacokinetic samples may be disposed of or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

6 SAFETY REPORTING AND MEDICAL MANAGEMENT

The principal investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative). The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE, SAE, ECI or AESI. For information on how to follow up AEs, see Section [6.5.2](#).

Care will be taken to not introduce bias when detecting AEs/SAEs/ECIs/AESIs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

6.1 Risks Associated with Acalabrutinib

The important identified risks of acalabrutinib are cytopenia, hemorrhage, atrial fibrillation/flutter, infections, and second primary malignancies. There is one important potential risk of hepatotoxicity. See the IB and the current local label for details of all important risks (identified and potential). Most of these risks are captured as ECIs.

The following summarizes the experience with acalabrutinib in hematological cancer studies. Full details regarding the clinical safety of acalabrutinib are presented in the acalabrutinib IB.

6.1.1 Contraindications

No contraindications are known for acalabrutinib.

6.1.2 Important Identified Risks

The following summarizes the experienced important identified risks observed with acalabrutinib in hematological cancer studies. Full details regarding the clinical safety of acalabrutinib are presented in the acalabrutinib IB.

6.1.2.1 Hemorrhage

Serious hemorrhagic events, including fatal events, have occurred in clinical studies with acalabrutinib.

The mechanism for hemorrhage is not well understood. Participants receiving antithrombotic agents may be at increased risk of hemorrhage. Use caution with antithrombotic agents and consider additional monitoring for signs of bleeding when concomitant use is medically necessary.

Consider the benefit-risk of withholding acalabrutinib for at least 3 days pre- and post-surgery.

Participants with hemorrhage should be managed per institutional guidelines with supportive care and diagnostic evaluations as clinically indicated.

6.1.2.2 Infections

Serious, including fatal, infections (bacterial, viral, and fungal) have occurred in clinical studies with acalabrutinib. The most frequently reported Grade ≥ 3 infection was pneumonia (PT). Across the acalabrutinib clinical development program (including patients treated with acalabrutinib in combination with other drugs), cases of HBV reactivation, aspergillosis, and PML have occurred.

Consider prophylaxis in participants who are at increased risk for opportunistic infections. Participants should be monitored for signs and symptoms of infection and treated as medically appropriate.

Participants with infection should be managed according to institutional guidelines with maximal supportive care and diagnostic evaluations as clinically indicated.

6.1.2.2.1 Progressive Multifocal Leukoencephalopathy

Serious or life-threatening occurrence of PML may occur in participants treated with acalabrutinib.

Signs and symptoms of PML may include cognitive and behavioral changes, language disturbances, visual disturbances, sensory deficits, weakness, and coordination and gait difficulties.

If PML is suspected, hold further study intervention (as applicable, based on risks in the IB or local prescribing information) until PML is excluded. A diagnostic evaluation may include (but is not limited to) the following:

- Neurologic consultation
- Brain MRI
- Polymerase chain reaction analysis for John Cunningham virus DNA in cerebrospinal fluid

If PML is confirmed, permanently discontinue study intervention (as applicable, based on risks in the IB or local prescribing information).

6.1.2.3 Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias, including neutropenia, anemia, and thrombocytopenia, have occurred in clinical studies with acalabrutinib. Monitor blood counts as specified in the SoA (see [Table 3](#)) and as medically appropriate.

Participants with cytopenias should be managed according to institutional guidelines with maximal supportive care and diagnostic evaluations as clinically indicated. Participants should be closely monitored as appropriate.

6.1.2.4 Second Primary Malignancies

Events of second primary malignancies, including non-skin carcinomas, have been reported in patients treated with acalabrutinib. The most frequently reported second primary malignancy was skin cancer.

Participants should be monitored for signs and symptoms of malignancy. Participants who develop a second primary malignancy should be managed according to institutional guidelines with diagnostic evaluations as clinically indicated, and it may be necessary for participants to permanently discontinue study intervention. Continuation of acalabrutinib treatment should be discussed with the medical monitor.

6.1.2.5 Atrial Fibrillation/Flutter

Events of atrial fibrillation/flutter have occurred in clinical studies with acalabrutinib, particularly in patients with cardiac risk factors, hypertension, diabetes mellitus, acute infections, or a previous history of atrial fibrillation.

Monitor for symptoms of atrial fibrillation and atrial flutter (eg, palpitations, dizziness, syncope, chest pain, dyspnea) and obtain an ECG as appropriate. Participants with atrial fibrillation should be managed per institutional guidelines or as clinically indicated.

6.1.3 Important Potential Risks

There is one important potential risk for acalabrutinib monotherapy. Information related to this important potential risk is presented below. Full details regarding the clinical safety of acalabrutinib are presented in the acalabrutinib IB.

6.1.3.1 Hepatotoxicity

The mechanism underlying hepatotoxicity of non-infectious etiology is currently unknown. The overall frequency of hepatotoxicity in acalabrutinib monotherapy pool is low, with the most frequently reported events being ALT and AST elevations. Following a comprehensive review of hepatotoxicity in the acalabrutinib clinical program, there was insufficient evidence to establish a causal association between hepatotoxicity and acalabrutinib due to the contribution of confounding factors, absence of clinical symptoms, and quick recovery without treatment for participants with transaminase elevations. There is limited evidence regarding hepatotoxicity of non-infectious etiology from literature for other BTK inhibitors.

6.1.4 Reproductive Toxicity

Acalabrutinib has been evaluated in a combined definitive fertility and EFD study in rats. Effects of acalabrutinib on embryofetal development was also evaluated in a definitive EFD study in rabbits. No effects on fertility or EFD were observed in rats at exposures 16 times the human exposure at the recommended dose. In rabbits, acalabrutinib was not teratogenic at any dose level. Decreased fetal body weight and delayed ossification were observed at exposure levels that produced maternal toxicity, which were approximately 4-fold greater than the human exposure levels at the recommended dose. Refer to the current IB for further details.

There has been one reported pregnancy in a participant exposed to acalabrutinib, in which the participant was exposed during the first trimester. Acalabrutinib was discontinued, and the participant gave birth to a live, full-term, male infant by cesarean section.

The potential for acalabrutinib to be excreted in breast milk of nursing mothers is unknown. In studies of lactating rats, acalabrutinib and its metabolite ACP-5862 were measured in milk and in the plasma of nursing pups on Postnatal Day 12.

There have been no positive genotoxicity findings during development of acalabrutinib. Additionally, based on modeled estimates of fetal exposures to active product ingredient levels in ejaculated material using assumptions for small molecules, direct embryofetal exposure (ie, female partner exposure following a vaginal dose of estimated seminal concentration) and male-mediated developmental risk with acalabrutinib treatment is considered to be very low, and risk mitigation measures for male-mediated developmental risk are therefore not required for acalabrutinib.

6.2 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a participant or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (for example, nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered. See [Table 5](#) for the timing of collection of AEs, SAEs, ECIs, and AESIs.

6.3 Definition of Serious Adverse Event

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, Follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires hospitalization or prolongs existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the participant or may require medical intervention to prevent one of the outcomes listed above

For further guidance on the definition of a SAE, see [Appendix A](#)

6.4 Definition of Events of Clinical Interest

The ECIs have been identified based on pre-clinical findings, emerging data from clinical studies relating to acalabrutinib, and pharmacological effects of approved BTK inhibitors. The AEs selected for dedicated analyses were evaluated using Standardized MedDRA Queries, where available, by system organ class, or by sponsor-defined baskets of MedDRA Adverse Event Grouped Terms. The ECI list is part of the SAP for all acalabrutinib studies and is used internally only. Please refer to the SAP for more detailed ECI definitions.

6.5 Recording of Adverse Events

6.5.1 Time Period for Collection of Adverse Events

Adverse events will be collected by the site from the time of signature of the ICF throughout the treatment period and including the Disease Follow-up period.

Serious adverse events will be recorded from the time of signing the ICF.

Serious adverse events occurring beyond the 30-day safety follow-up period and considered by the investigator to be possibly related to the study intervention will also be reported. If the investigator becomes aware of an SAE with a suspected causal relationship to the IMP that occurs after the end of the clinical study in a treated participant, the investigator shall, without undue delay, report the SAE to AstraZeneca.

Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment or other assessment/visit as appropriate in the study, are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Further clarifications are described in [Table 5](#).

Table 5 Guidance for Reporting Adverse Events

Period	Non-serious AEs	SAEs
Signing of ICF – First dose of study intervention	Not reported (recorded as medical history)	Report all
First dose of study intervention – 30 days after last dose of study intervention or the start of new anticancer therapy (whichever comes first)	Report all	Report all
Post-30 days after last dose of study intervention or the start of new anticancer therapy (whichever comes first)	Not reported	Report related

AE = adverse event; ICF = informed consent form; SAE = serious adverse event.

6.5.2 Follow-up of Unresolved Adverse Events

All SAEs that occur during the reporting period should be followed to resolution or until the investigator assesses the participant as stable, or until the participant is lost to follow-up or

withdraws consent. Resolution/stable means the participant has returned to baseline state of health, or the investigator does not expect any further improvement or worsening of the event.

If an SAE/ECI/AESI is present at the last study visit, the SAE/AESI should be followed to resolution or until the investigator assesses the participant as stable, or the participant is lost to follow-up or withdraws consent. The sponsor retains the right to request additional information for any participant with ongoing AE/SAE/ECI/AESI at the end of the study, if judged necessary.

6.5.3 Variables

The following variables will be collected for each AE/ECI:

- Adverse event (verbatim)
- The date when the AE started and stopped
- Severity
- Whether the AE is serious or not
- Investigator causality rating against the study intervention (yes or no)
- Action taken regarding IP
- Outcome

In addition, the following variables will be collected for SAEs/AESIs:

- Date AE met criteria for seriousness
- Date investigator became aware of SAE/AESI
- Seriousness criteria
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

Adverse event severity will be graded by the investigator according to the NCI CTCAE (version 5.0).

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.3. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.3. On the

other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.3.

6.5.4 Causality Collection

The investigator will assess causal relationship between the study intervention and each AE, and answer ‘yes’ or ‘no’ to the question ‘Do you consider that there is a reasonable possibility that the event may have been caused by the IP?’

For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as yes.

A guide to the interpretation of the causality question is found in [Appendix A](#).

6.5.5 Adverse Events Based on Examinations and Tests

The results from the CSP-mandated laboratory tests and vital signs will be summarized in the CSR. Deterioration as compared with baseline in protocol-mandated laboratory values, vital signs, or other physical assessments should be reported only if the deterioration fulfills any of the SAE criteria or is the reason for discontinuation of treatment with the study intervention.

If deterioration in a laboratory value, vital sign, etc. is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated result will be considered as additional information. Wherever possible the reporting investigator should use the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, a clinically relevant deterioration in non-mandated parameter should be reported as an AE.

Any new or worsening clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

6.5.6 Hy’s Law

Cases in which a participant shows elevation in liver biochemistry may require further evaluation and occurrences of AST or ALT $\geq 3.0 \times \text{ULN}$ together with TBL $\geq 2.0 \times \text{ULN}$ may need to be reported as SAEs. See [Appendix D](#) for further instruction on cases of increases in liver biochemistry and evaluation of Hy’s Law.

6.5.7 Disease Progression

Disease progression itself is not considered an AE; however, signs and symptoms of disease may be recorded as AEs or SAEs.

Progressive disease during or after therapy is characterized by at least 1 of the following:

- Lymphadenopathy: appearance of any new lesion such as enlarged LNs (≥ 1.5 cm), splenomegaly, hepatomegaly, or other organ infiltrates or,
- Lymphadenopathy: an increase by $\geq 50\%$ in greatest determined diameter of any previous site (≥ 1.5 cm) or,
- An increase in the spleen size by $\geq 50\%$ or the de novo appearance of splenomegaly or,
- An increase in the liver size of $\geq 50\%$ of the extent enlargement of the liver below the costal margin defined by palpation, or the de novo appearance of hepatomegaly or,
- An increase in the number of blood lymphocytes by 50% or more with at least $5 \times 10^9/L$ B lymphocytes or,
- Transformation to a more aggressive histology (Richter syndrome or Richter transformation) or,
- Occurrence of cytopenia (neutropenia, anemia, or thrombocytopenia) directly attributable to CLL and unrelated to autoimmune cytopenia.

Progressive disease was defined according to [Hallek et al. 2018](#).

6.6 Reporting of Serious Adverse Events and Adverse Events of Special Interest

6.6.1 Reporting of Serious Adverse Events

All SAEs must be reported whether or not considered causally related to the IMP. All SAEs will be recorded in the eCRF.

If any SAE occurs during the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives within 1 day, ie, immediately **but no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately **but no later than 24 hours** of when he or she becomes aware of it.

6.6.2 Adverse Events of Special Interest

An AESI is an AE of scientific and medical interest specific to understanding of a study intervention and may require close monitoring and rapid communication to AstraZeneca by the investigator. An AESI may be serious or non-serious. The reporting of AESIs allows ongoing surveillance of these events to characterize and understand them in association with the use of a study intervention.

Adverse events of special interest will be recorded on the eCRF using a recognized medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the investigator for severity, relationship to the study intervention, possible etiologies, and whether the event meets the criteria for an SAE and therefore requires immediate notification to AstraZeneca. If an AE evolves into a condition that meets the regulatory definition of “serious,” it will be reported as described in Section 6.6.1 (Reporting of SAEs).

Based on available pre-clinical and clinical data, review of cumulative literature, reported toxicities for the same class of agents and biological plausibility, the following events are considered to be AESIs:

- Ventricular arrhythmias (eg, ventricular extrasystoles, ventricular tachycardia, ventricular arrhythmia, and ventricular fibrillation)

6.6.3 Expedited Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

Initial SAE reports and Follow-up information will be reported using the protocol-specific electronic data capture system, according to the instructions provided in the investigator site file. If electronic SAE reporting is not available, paper SAE forms must be emailed or faxed to the sponsor’s drug safety group, or designee. The sponsor may request follow-up and other additional information from the investigator (eg, hospital admission/discharge notes and laboratory results). Whenever possible, AEs/SAEs should be reported by diagnosis term, not as a constellation of symptoms.

Death due to disease progression should be recorded on the appropriate form in the electronic data capture system. If the primary cause of death is disease progression, the death due to disease progression should not be reported as an SAE. If the primary cause of death is something other than disease progression, then the death should be reported as an SAE with the primary cause of death as the event AE term, as death is typically the outcome of the event, not the event itself. The primary cause of death on the autopsy report should be the term reported. Autopsy and postmortem reports must be forwarded to the sponsor’s drug safety group, or designee, as outlined above.

If study intervention is discontinued because of an SAE, this information must be included in the SAE report.

An SAE may qualify for mandatory expedited reporting to regulatory authorities if the SAE is attributable to the IP (or if a causality assessment is not provided for the SAE, in which case a default of 'related' may be used for expedited reporting purposes) and the SAE is not listed in the current Reference Safety Information for each study intervention (ie, an unexpected event). Regulatory authority reporting performed by the sponsor is in accordance with local reporting requirements. For EU countries, expedited submission of individual case safety reports to the concerned regulatory authority for suspected unexpected SUSARs occurs within 7 calendar days of awareness for fatal/life-threatening SUSARs and within 15 calendar days of awareness for other SUSARs. The clock start date for regulatory reporting is the date it is first received by any sponsor personnel or person working on behalf of the sponsor. In this case, sponsor's drug safety group /designee will forward a formal notification describing the SUSAR to all investigators. Each investigator must then notify his or her IRB/IEC of the SUSAR.

6.7 Overdose

Study intervention overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study intervention is not an AE unless it results in untoward medical effects. An overdose without associated symptoms is only reported on the Overdose eCRF module. If the associated AE fulfills serious criteria, the event should be reported to the sponsor immediately (ie, no more than 24 hours after learning of the event).

If an overdose on the study intervention occurs during the study, then the investigator or other site personnel must inform the appropriate sponsor representative immediately, or **no later than 24 hours** of when he or she becomes aware of it. The designated sponsor representative will work with the investigator to ensure that all relevant information is provided to the sponsor's participant safety data entry site.

For overdoses associated with an SAE, the standard reporting timelines apply, see Section 6.6. For other overdoses, reporting must occur within 30 days.

For any participant experiencing an overdose of any study intervention, observation for any symptomatic side effects should be instituted, and vital signs and biochemical and hematologic parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated. If the overdose ingestion is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered. Additional information on overdose, including management or guidance, that is available in the IB should also be considered and followed, as applicable.

6.8 Pregnancy

The investigator should report all pregnancies and pregnancies in the partners of participants within 24 hours using the Pregnancy Report Form. This form should be faxed or emailed to the sponsor's appropriate sponsor drug safety representatives. Any pregnancy-associated SAE must be reported to the sponsor, according to the usual timelines and directions for SAE reporting.

Any uncomplicated pregnancy that occurs with the participant or with the partner of a treated participant during this study will be reported. All pregnancies and partner pregnancies that are identified during or after this study, wherein the estimated date of conception is determined to have occurred from the time of consent to 2 days after the last dose of study intervention will be reported, followed to conclusion, and the outcome reported, if the participant or partner is willing to participate in Follow-up.

A pregnancy itself is not regarded as an AE unless there is suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Likewise, elective abortions without complications are not considered AEs. Any SAEs associated with pregnancy (eg, congenital abnormalities/birth defects/spontaneous miscarriage or any other serious events) must additionally be reported as such using the SAE report form.

Participants should be instructed to immediately notify the investigator of any pregnancies. Any female participants receiving study intervention who become pregnant must immediately discontinue study intervention. The investigator should counsel the participant, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Upon completion of the pregnancy, additional information on the mother, pregnancy, and baby will be collected and sent to the sponsor.

6.9 Medication Error, Drug Abuse, and Drug Misuse

6.9.1 Timelines

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 calendar day**, ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within **1** (initial fatal/life-threatening or follow-up fatal/life-threatening) **or 5 calendar days** (other serious initial and follow-up), if there is an SAE associated with the event of medication error, drug abuse, or misuse (see Section 6.6), and **within 30 days** for all other events.

6.9.2 Medication Error

For the purposes of this clinical study, a medication error is an **unintended** failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition and examples of medication error can be found in [Appendix A](#).

6.9.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in [Appendix A](#).

6.9.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of drug misuse can be found in [Appendix A](#).

7 INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of Investigational Product

Study intervention in this study refers to acalabrutinib. Acalabrutinib is (S)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)-imidazo[1,5- α]pyrazin-1-yl)-N-(pyridin-2-yl)-benzamide. Acalabrutinib is manufactured according to current Good Manufacturing Process regulations and will be provided to the investigational site by the sponsor or designee.

Acalabrutinib treatment product is provided as hard gelatin capsules for oral administration. Each capsule contains 100 mg of acalabrutinib. All formulation excipients are compendial and are commonly used in oral formulations. Formulation details are provided in the acalabrutinib IB.

7.2 Dose and Treatment Regimens

Study intervention (acalabrutinib) is intended to be administered as one 100 mg capsule taken orally bid with 8 ounces (approximately 240 mL) of water. Study intervention may be taken with or without food. The capsules should be swallowed intact, and participants should not attempt to open capsules or dissolve them in liquid.

It is recommended that study intervention be taken as close to the scheduled time as possible (preferably within ± 1 hour). However, if a dose is missed, it can be taken up to 3 hours after the scheduled time with a return to the normal schedule with the following dose. If it has been > 3 hours, the dose should not be taken, and the participant should take the next dose at the next scheduled time. The missed dose will not be made up and must be returned to the site at the next scheduled visit. Participants will record the missed dose and reason in their drug diary.

Investigators are prohibited from supplying study intervention to any participants not properly enrolled in this study. The investigator must ensure that participants receive study intervention only from personnel who fully understand the procedures for administering the drug.

See Section 4.3 for information about post-study acalabrutinib treatment.

7.3 Labeling

The acalabrutinib capsules are packaged in opaque high-density polyethylene plastic bottles with labels bearing the appropriate label text as required by appropriate local governing regulatory agencies.

7.4 Storage

Acalabrutinib should be stored according to the instructions on the label affixed to the package of the drug product (store below 30°C [86°F]). The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

If a drug shipment arrives damaged, or if there are any other drug complaints, a Product Complaint Form should be completed and emailed or faxed to the sponsor or the sponsor's representative.

Study intervention should be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the instructions on the label affixed to the package of the drug product, with access limited to the investigator and authorized site staff.

7.5 Compliance

For study intervention taken in the clinic, participants should take the dose from the study intervention dispensed for them for that particular time period. All other study interventions will be taken at home. Participants will receive a drug diary to record the specific time each dose was taken and to record reasons for any missed doses. Participant compliance will be assessed at each study visit by the investigator and/or study personnel. The participant will be instructed to bring the diary and any remaining study intervention to the clinic at their next visit. The study staff will review the diary and ask the participant if all the capsules were administered. Any remaining or

returned capsules will be counted and recorded. Returned capsules must not be re-dispensed to another participant.

The drug diary should be completed until the last dose of study intervention.

There is no “limit” to the number of doses a participant can miss; that is, some participants might have “intermittent” missed doses and in these cases based on the investigator’s assessment of no disease progression and/or safety issue for the participant, the participant may continue in the study. If a participant does not take the study medication for > 28 days, then the participant must be withdrawn from the study, unless continued administration is approved by the medical monitor.

7.6 Accountability

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

7.7 Concomitant Medications

7.7.1 Permitted Concomitant Medications

Standard supportive care medications are permitted; this includes premedication to decrease the risk of tumor lysis syndrome, infusion-related reaction, infections, and other risks or toxicities as described in the acalabrutinib IB.

Additional bacterial/viral/fungal prophylaxis for participants at risk for infections, particularly for participants who develop severe neutropenia, is allowed per institutional standards and at the discretion of the managing physician.

Use of hematopoietic growth factors is permitted per the ASCO guidelines ([Smith et al. 2015](#)) or per institutional guidelines.

7.7.2 Prohibited or Restricted Concomitant Medications

Any chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy for treating CLL is prohibited. High-dose corticosteroids used to treat the underlying CLL are not permitted on study prior to discontinuation of study intervention.

Warfarin or equivalent vitamin K antagonists are prohibited.

Immunization with a live vaccine is prohibited within 4 weeks before study intervention and during study intervention.

The concomitant use of strong inhibitors/inducers of CYP3A with acalabrutinib should be avoided when possible (see [Appendix E](#)) for known strong in vivo inhibitors and inducers of CYP3A). Participants requiring long-term (> 1 week) treatment with a strong CYP3A inhibitor/inducer are excluded from the study (see Exclusion Criterion 23). In addition, the use of strong or moderate CYP3A inhibitors or inducers within 7 days of the first dose of study intervention is prohibited. If a participant requires short-term treatment (≤ 7 days) with a strong CYP3A inhibitor, acalabrutinib treatment should be interrupted. If the participant requires treatment with a moderate CYP3A inhibitor, the acalabrutinib dose should be reduced to 100 mg qd. Coadministration of strong CYP3A inducers should be avoided. If a participant requires treatment with a strong CYP3A inducer, the acalabrutinib dose should be increased to 200 mg bid.

Use of proton-pump inhibitors, H₂ receptor antagonists, or antacids while taking acalabrutinib is not recommended due to a potential decrease in study intervention exposure. If treatment with a gastric acid reducing agent is required, use of a H₂-receptor antagonist (2 hours after acalabrutinib) or antacid (2 hours before or 2 hours after acalabrutinib) should be considered. Coadministration of acalabrutinib with proton-pump inhibitors should be avoided.

The concomitant use of acalabrutinib with BCRP substrates (eg, prazosin, glyburide, nitrofurantoin, dipyridamole, statins, and cimetidine) may increase exposure to the BCRP substrates by inhibition of intestinal BCRP, and therefore should be avoided.

8 STATISTICAL ANALYSES

8.1 Statistical Considerations

Analyses will be performed by the sponsor or its representatives. A comprehensive SAP will be developed and finalized before first ISA and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan will be reported in the CSR.

8.2 Sample Size Estimate

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.

Participants in the UK will not be enrolled into the TN cohort. Participants in the US will not be enrolled into the prior ibrutinib therapy cohort.

In a sample of 301 participants with CLL treated with acalabrutinib from Study ACE-CL-001, the participant incidences of the safety events are presented in [Table 6](#).

Table 6 Incidences of Safety Events 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.

Source: Study ACE-CL-001

The AE with the lowest incidence among R/R participants observed in [Table 6](#) was 2.2%. There is 98.8% probability of observing ≥ 1 event in a sample of 200 participants if the true incidence were 2.2%. The AE with the lowest incidence among TN participants observed in [Table 6](#) was 1%. There is 95.1% probability of observing ≥ 1 event in a sample of 300 participants if the true incidence were 1%.

[Table 7](#) provides an illustration of the level of precision (exact Clopper-Pearson 95% CI) for an AE with varying observed incidence.

Table 7 Level of Precision (Exact 95% Confidence Interval) for Adverse Events with Varying Observed Incidence

Number of Participants	Observed Percentage in Population							
	0%	1%	3%	5%	10%	30%	50%	70%
30	(0.0%, 11.6%)	(0.0%, 17.2%)	(0.0%, 17.2%)	(0.1%, 22.1%)	(2.1%, 26.5%)	(14.7%, 49.4%)	(31.3%, 68.7%)	(50.6%, 85.3%)
70	(0.0%, 5.1%)	(0.0%, 7.7%)	(0.3%, 12.0%)	(0.9%, 14.0%)	(4.1%, 19.5%)	(19.6%, 42.1%)	(37.8%, 62.2%)	(57.9%, 80.4%)
100	(0.0%, 3.6%)	(0.0%, 5.4%)	(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%)	(6.8%, 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%, 7.3%)	(7.5%, 13.0%)	(26.0%, 34.2%)	(45.5%, 54.5%)	(65.8%, 74.0%)

Note: Clopper-Pearson exact 95% confidence interval. When the expected number of participants is not an integer, it is rounded down for the lower limit, and rounded up for the upper limit.

8.3 Definitions of Analysis Populations

The populations for statistical analyses and study summary are defined as follows:

- Safety Analysis Set: 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. More details for participants included in statistical analysis of each specific efficacy endpoint will be provided in SAP.
- Pharmacokinetic Analysis Set: participants in the SAF who have ≥ 1 evaluable post-treatment PK value. The PKAS will be used for all summaries of PK data.

8.4 Endpoints for Analyses

Study endpoints are described in Section 2 along with the corresponding study objectives.

8.5 Methods for Statistical Analyses

8.5.1 Efficacy Analyses

The secondary objective of this study is to evaluate efficacy of acalabrutinib in the broad CLL population. All cohorts will be separately assessed for response by the investigator according to iwCLL 2018 criteria ([Hallek et al. 2018](#)).

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.

Duration of response will be 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 DCO or have unknown status will have DOR right-censored at the time of their last disease assessment on or before DCO. Kaplan-Meier estimates and corresponding 2-sided 95% CIs will be calculated for the median and quartiles.

Progression-free survival will be defined as the interval from the start of study intervention to the earlier of the first documentation of disease progression or death from any cause. Participants who are progression-free and alive at the time of DCO or have unknown status will have PFS right-censored at the time of their last disease assessment on or before DCO. Kaplan-Meier estimates and corresponding 2-sided 95% CIs will be calculated for the median and quartiles.

Descriptive statistics will be provided for the EORTC-QLQ-C30 and PRO-CTCAE for each assessment time point. Additional analyses of PRO data will be described in the statistical analyses plan.

8.5.2 Safety Analyses

The primary objective of this study is to evaluate safety in the broad CLL population by describing rate of SAEs, AESIs, rate of Grade ≥ 3 AEs, rate of ECIs (including cardiac rhythm disorders, opportunistic infections, interstitial lung disease, major hemorrhage, cytopenias, and second primary malignancies), and the frequency, severity, and relatedness of all AEs including Grade ≥ 3 AEs, SAEs, AESI, ECIs, and AEs leading to treatment discontinuation.

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 intervention. Missing or partial start and end dates for AEs and concomitant medications will be imputed according to prespecified, conservative imputation rules. The SAP will describe approaches for other missing data.

Detailed tabulations of safety data will be provided for all participants receiving the study intervention. Summary of other additional parameters will be provided where appropriate.

Adverse Events

AEs will be graded by the investigator according to the NCI CTCAE (version 5.0). Each AE verbatim term will be coded to an SOC and a preferred term using the MedDRA.

The number and percentage of participants with treatment-emergent AEs will be summarized. In addition, treatment-emergent AEs will also be summarized by severity and relationship to study intervention. ECIs and AESIs will be summarized similarly to treatment-emergent AEs.

Clinical Laboratory Tests

For gradable parameters, a summary of worst postbaseline toxicity grade will be provided in the treatment-emergent period by worst toxicity grade (any Grade and Grade 3 or 4). The difference in percentages will be displayed. Only participants with a baseline and at least one postbaseline value will be included in the denominator.

Analysis of Lymphocytosis

For all participants with baseline and any postbaseline ALC measurements, ALC at peak summary will be provided.

Lymphocytosis will be defined as an ALC > 5000 cells/ μ L and an increase above baseline. The number of participants with ≥ 1 occurrence of lymphocytosis will be summarized. For participants with lymphocytosis, resolution of lymphocytosis will be defined as 1) a decrease of ALC value to the baseline level or lower, or 2) an achievement of ALC value that is below

or equal to 5000 cells/ μ L, whichever occurs first. For participants with lymphocytosis, the ALC at peak and time to peak ALC will be assessed. The data will be summarized by descriptive statistics.

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 postbaseline assessment to the earliest date on which a subsequent ALC value met the resolution criteria.

Analysis of Serum Immunoglobulins

For each serum immunoglobulin variable (IgA, IgG, and IgM), descriptive statistics will be presented at each scheduled postbaseline assessment. Participants who received IVIG on the study will be excluded from the summary for IgG.

Vital Signs

Summary statistics (mean, standard deviation, median, and range) will be produced for baseline, maximum, and minimum values of body temperature, heart rate, respiratory rate, and blood pressure over time.

8.5.3 Demographics and Baseline Characteristics

Participant demographics and baseline characteristics will be summarized. Concomitant and prior medications will be coded (according to the World Health Organization Drug Dictionary) and tabulated.

8.5.4 Eastern Cooperative Oncology Group

Eastern Cooperative Oncology Group performance status scores will be summarized using a shift table. The shifts in scores from baseline to worst ECOG score on study intervention will be summarized.

8.5.5 Pharmacokinetic Analyses

Plasma concentrations of acalabrutinib and ACP-5862 will be tabulated for each participant by visit and time point. Summary statistics (eg, mean, median, standard deviation, percent coefficient of variation) and plots will be presented, as appropriate.

Additional analyses may be conducted by combining PK and other relevant data across studies. Potential correlations of exposure with safety and efficacy outcomes may be explored as warranted by the data. These analyses may be reported separately from the CSR.

Details of the PK parameters and the analyses assessed are provided in the SAP.

8.5.6 Interim Safety Analysis

Interim safety analyses will be performed to review accumulating safety data periodically and ensure that participants are not exposed to any undue risk. Safety assessment 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 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.

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.

The SAP will describe the planned interim analyses in greater detail.

8.5.7 Data Safety Monitoring Committee

A DSMC will be set up for this study to monitor safety on an ongoing basis and perform periodic assessments of participant safety data. The DSMC meeting will take place by teleconference annually after first interim analysis. The first DSMC meeting occurred after the first DCO, which was after approximately 100 participants had been treated in the study and followed up for approximately 12 cycles of study intervention or until discontinuation from the study for whatever reason. The second ISA was performed after a period of 12 months after the first ISA. The final analyses for this study will be performed after all participants complete 48 cycles (or discontinued before) including 30 days of Follow-up and the database will be locked. Modified and/or additional safety reviews may be added based on recommendation by the DSMC, based on the first safety analysis review after full study enrollment. Full details of the DSMC procedures and processes can be found in the DSMC charter.

9 STUDY AND DATA MANAGEMENT

9.1 Training of Study-site Staff

Before the first participant is entered into the study, the CRO will review and discuss the requirements of the CSP and related documents with the investigational staff and train them in any study specific procedures and system(s) used.

The principal investigator will ensure that appropriate training relevant to the study is given to all staff, and that any new information relevant to the performance of this study is forwarded to the staff involved. In addition, the principal investigator will maintain a record of all individuals involved in the study (medical, nursing, and other staff).

9.2 Monitoring of the Study

During the study, a sponsor representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator.
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the CSP, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the laboratory manual and that study intervention accountability checks are being performed.
- Perform source data verification (a comparison of the data in the eCRFs with the participant's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participants. This will require direct access to all original records for each participant (eg, clinic charts).
- Ensure withdrawal of informed consent to the use of the participant's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the participant.

The sponsor representative will be available between visits if the investigator or other staff at the site needs information and advice about the study conduct.

9.2.1 Source Data

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents will be filed at the study site.

Data reported on the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

For all applicable countries following EU regional guidance on the management of COVID-19 in clinical studies, refer to [EMA 2022](#) for further guidance on changes of monitoring, including remote source data verification.

9.2.2 Study Agreements

The principal investigator at each site should comply with all the terms, conditions, and obligations of the CSP, or equivalent, for this study.

Agreements between the sponsor and the principal investigator should be in place before any study-related procedures can take place, or participants are enrolled.

9.2.3 Archiving of Study Documents

The investigator must follow the principles outlined in the CSP.

Records will be retained per local regulations.

9.3 Study Timetable and End of Study

For the purpose of Clinical Trial Transparency, the definition of the end of the study differs under FDA and EU regulatory requirements:

European Union requirements define study completion as the last visit of the last participant for any protocol-related activity.

Food and Drug Administration requirements define 2 completion dates:

Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the prespecified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the prespecified protocol or is terminated.

A participant is considered to have completed the study if they have completed all phases of the study, including the last scheduled procedure/assessment shown in the SoAs.

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. Participants continuing on study after 48 cycles (in regions where acalabrutinib has not received regulatory approval) should continue to be followed; therefore, additional study time will be accrued for those participants (the amount of time will vary by participant).

Data observed after final DCO will not be described in the final CSR except those data for end of treatment or end of study. After the final DCO, participants ongoing on study intervention will be treated per standard of care.

For participants who do continue to receive acalabrutinib treatment beyond the time of this final DCO, investigators will continue to report all SAEs to AstraZeneca Patient Safety until 30 days after study intervention is discontinued, in accordance with Section 6.6. If an investigator learns of any AEs or SAEs, including death, at any time after the final DCO and he/she considers there is a reasonable possibility that the event is causally related to the study intervention, the investigator should notify AstraZeneca, Patient Safety. Additionally, as stated in Section 6.5, any SAE or non-serious AE that is ongoing at the time of this final DCO, must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the participant is lost to follow-up.

The study may be terminated at individual sites if the study procedures are not being performed according to GCP, or if recruitment is slow. The sponsor may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with acalabrutinib.

9.4 Data Management

Data management will be performed by a CRO according to the data management plan.

The data collected through third-party sources will be obtained and reconciled against study data reported on the eCRFs.

AEs and medical/surgical history will be classified according to the terminology of the latest version of MedDRA. Medications will be classified according to the World Health Organization Drug Dictionary. All coding will be performed by the CRO.

Data queries will be raised for inconsistent, improbable, or missing data. History of all entries to the study database will be available in an audit trail.

The data will be validated as defined in the data management plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The data management plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

The final database will be locked when all data have been validated, coded, and signed for by the investigator.

Serious Adverse Event Reconciliation by the Sponsor's Medical Safety Team

Serious adverse event reconciliation reports are produced and reconciled with the patient safety database and/or the investigational site.

Data Associated with Human Biological Samples

Data associated with biological samples will be transferred from laboratories internal or external to the sponsor.

10 ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements and the sponsor's policy on bioethics and human biological samples.

10.2 Participant Data Protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

The sponsor will not provide individual genotype results to participants, any insurance company, any employer, their family members, general physician, unless required to do so by law.

Precautions are taken to preserve confidentiality and prevent genetic data from being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a participant. For example, in the case of a medical emergency, a sponsor physician or an investigator might know a participant's identity and also have access to his or her genetic data. Also, regulatory authorities may require access to the relevant files, though the participant's medical information and the genetic files would remain physically separate.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study archiving or as required by local regulations after study completion, unless local regulations or institutional policies require a different retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.3 Ethics and Regulatory Review

An IRB/IEC should approve the final CSP, including the final version of the ICF and any other written information and/or materials to be provided to the participants. The investigator will ensure the distribution of these documents to the applicable IRB/IEC, and to the study-site staff.

The opinion of the IRB/IEC should be given in writing. The investigator should submit the written approval to the sponsor before enrollment of any participant into the study.

The IRB/IEC should approve all advertising used to recruit participants for the study.

The sponsor should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the CSP should be re-approved by the IRB/IEC annually.

Before enrollment of any participant into the study, the final CSP, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

The sponsor will handle the distribution of any of these documents to the national regulatory authorities.

The sponsor will provide regulatory authorities, IRBs/IECs, and principal investigators with safety updates/reports according to local requirements.

Each principal investigator is responsible for providing the IRB/IEC with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. The sponsor will provide this information to the principal investigator so that he/she can meet these reporting requirements.

10.4 Informed Consent

The principal investigator at each site will:

- Ensure each participant or legally authorized representative (if allowed per local regulations) is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study.
- Ensure each participant or legally authorized representative (if allowed per local regulations) is notified that they are free to discontinue from the study at any time.
- Ensure that each participant or legally authorized representative (if allowed per local regulations) is given the opportunity to ask questions and allowed time to consider the information provided.
- Ensure each participant or legally authorized representative (if allowed per local regulations) provides signed and dated informed consent before conducting any procedure specifically for the study.
- Ensure the original, signed ICF(s) is/are stored in the investigator's study file.
- Ensure a copy of the signed ICF is given to the participant or legally authorized representative (if allowed per local regulations).
- Ensure that any incentives for participants who participate in the study as well as any provisions for participants harmed as a consequence of study participation are described in the ICF that is approved by an IRB/IEC.

Future research is important to advance science and public health. With specific participant consent, participant's coded data collected throughout the study and leftover biosamples from the PK analysis portion of this study may be used for scientific health-related research to find new ways to detect, treat, prevent, or cure health problems. They may also be used jointly with information from other sources outside typical clinical research settings, for example, from public research databases. However, they will not be combined with other information in a way that could identify an individual participant. Some research projects may require the analysis of genetic information.

10.5 Changes to the Clinical Study Protocol and Informed Consent Form

Study procedures will not be changed without the agreement of the sponsor.

If there are any substantial changes to the CSP, then these changes will be documented in a new version of the study protocol.

The new version of the CSP is to be approved by the relevant IRB/IEC and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for new versions of CSPs.

The sponsor will distribute any new versions of the CSP to each principal investigator. For distribution to IRB/IEC, see Section [10.3](#).

If a change to a CSP requires a change to a site's ICF, the sponsor and the site's IRB/IEC are to approve the revised ICF before the revised form is used.

10.6 Audits and Inspections

Authorized representatives of the sponsor, a regulatory authority, or an IRB/IEC may perform audits or inspections at the site, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the CSP, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact the sponsor immediately if contacted by a regulatory agency about an inspection at the site.

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12 APPENDICES

Appendix A Additional Safety Information

Further Guidance on the Definition of a SAE

Definitions of Serious Adverse Event

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, Follow-up), that fulfills 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above

In tumor-related SAEs, tumors must be new tumors (ie, it is *not* the tumor for which entry into the study is a criterion and that is being treated by the IP under study and is not the development of new or progression of existing metastasis to the tumor under study).

Malignant tumors that – as part of expected, if rare, progression – undergo transformation (eg, Richter’s transformation of B-cell CLL into DLBCL) should not be considered a new malignant tumor. In other SAEs, all definitions apply.

Life-threatening

‘Life-threatening’ means that the participant was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the product would result in the participant’s death. ‘Life-threatening’ does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Adverse Event of Special Interest

The following event is considered an AESI:

- Ventricular arrhythmias (eg, Torsade de pointes, ventricular extrasystoles, ventricular tachycardia, ventricular arrhythmia, ventricular fibrillation, ventricular flutter, and ventricular tachyarrhythmia).

Hospitalization

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability, or incapacity, but may jeopardize the participant or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used. For example:

- Angioedema not severe enough to require intubation but requiring IV hydrocortisone treatment.
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine.
- Intensive treatment in an emergency room or at home for allergic bronchospasm.
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization.
- Development of drug dependency or drug abuse.

Intensity Rating Scale:

- Mild (awareness of sign or symptom, but easily tolerated).
- Moderate (discomfort sufficient to cause interference with normal activities).
- Severe (incapacitating, with inability to perform normal activities).

The grading scales found in the revised NCI CTCAE latest version will be used for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (<https://ctep.cancer.gov>).

A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a ‘reasonable possibility’ that an AE may have been caused by the treatment.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? The sponsor would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of ‘related’ is made if following a review of the relevant data, there is evidence for a ‘reasonable possibility’ of a causal relationship for the individual case. The expression ‘reasonable possibility’ of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as ‘not related’.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Medication Error, Drug Abuse, and Drug Misuse

Medication Error

For the purposes of this clinical study, a medication error is an unintended failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug but rather a human- or process-related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error:

- Occurred
- **Was identified and** intercepted before the participant received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error, eg, medication prepared incorrectly even if it was not actually given to the participant
- Drug not administered as indicated, eg, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the refrigerator when it should be at room temperature
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which led to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

Drug Abuse

For the purposes of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

Appendix B International Airline Transportation Association (IATA) 6.2 Guidance Document

Labeling and Shipment of Biohazard Samples

The IATA classifies biohazardous agents into 3 categories.

(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).

For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B, or Exempt. There is no direct relationship between risk groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt – all other materials with minimal risk of containing pathogens

- Clinical study samples will fall into Category B or Exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging
(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry ice content**
- International Airline Transportation Association compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable.
- Samples routinely transported by road or rail are subject to local regulations, which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix C Handling of Human Biological Samples

Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The investigator at each center keeps full traceability of collected biological samples from the participants while in storage at the center until shipment or disposal (where appropriate) and records relevant processing information related to the samples while at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

Withdrawal of Informed Consent for Donated Biological Samples

AstraZeneca ensures that biological samples are destroyed at the end of a specified period as described in the informed consent.

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The investigator:

- Ensures participant's withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organizations holding the samples are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented, and the study site is notified.

Appendix D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

Introduction

This appendix describes the process to be followed to identify and appropriately report PHL cases and HL cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the study the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a participant meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits, including central and all local laboratory evaluations, even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory and/or elevated TBL from a local laboratory).

The investigator will also review AE data for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The investigator participates together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the IP.

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law

Aspartate aminotransferase or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ ULN at any point during the study following the start of study intervention, regardless of an increase in ALP.

Hy's Law

Aspartate aminotransferase or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ ULN, where no other reason, other than the IP can be found to explain the combination of increases eg, elevated ALP indicating cholestasis, viral hepatitis, or another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Identification of Potential Hy's Law Cases

To identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT $\geq 3 \times$ ULN
- AST $\geq 3 \times$ ULN
- TBL $\geq 2 \times$ ULN

Local Laboratories Being Used:

The investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the sponsor representative/medical monitor by telephone and report the case as an SAE of PHL; seriousness criteria "Important medical event" and causality assessment "yes/related" or in accordance with the CSP as appropriate.
- Determine whether the participant meets PHL criteria (see D2 for definition) by reviewing laboratory reports from all previous visits.
- Promptly enter the laboratory data into the laboratory eCRF.

Follow-up

Potential Hy's Law Criteria Not Met

If the participant does not meet PHL criteria the investigator will:

- Inform the AstraZeneca representative that the participant has not met PHL criteria.
- Perform Follow-up on subsequent laboratory results according to the guidance provided in the CSP.

Potential Hy's Law Criteria Met

If the participant does meet PHL criteria, the investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study intervention.
- Notify the AstraZeneca representative who will then inform the central study team.
- Within 1 day of PHL criteria being met, the investigator will report the case as an SAE of PHL; serious criteria 'important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.
- For participants that met PHL criteria prior to starting IP, the investigator is not required to submit a PHL SAE unless there is a significant change in the participant's condition.
- The study physician contacts the investigator, to provide guidance, discuss and agree an approach for the study participants' Follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the investigator will:
 - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes Follow-up SAE Form as required.
 - Investigate the etiology of the event and perform diagnostic investigations as discussed with the study physician. This includes deciding which of the tests available in the HL lab kit should be used.
 - Complete the 3 Liver eCRF Modules as information becomes available.

A 'significant' change in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the study physician if there is any uncertainty.

Review and Assessment of Potential Hy's Law Cases

The instructions in this section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality is initially detected, the study physician contacts the investigator to review available data, to agree whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IP and to ensure that timely analysis and reporting to health authorities within 15 calendar days from the date PHL criteria were met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and, subsequently, whether the AE meets the criteria for an SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.
- If the alternative explanation is an AE/SAE, update the previously submitted PHL SAE and AE eCRFs accordingly with the new information (reassessing event term, causality, and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IP, then:

- Send updated SAE (report term “Hy’s Law”) according to the sponsor’s standard processes:
 - The “Medically Important” serious criterion should be used if no other serious criteria apply.
 - Because there is no alternative explanation for the HL case, a causality assessment of “related” should be assigned.

If there is an unavoidable delay of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provide any further update to the previously submitted SAE of PHL (report term now “Hy’s Law case”), ensuring causality assessment is related to IP and seriousness criteria are medically important, according to CSP process for SAE reporting.
- Continue Follow-up and review according to the agreed plan. After the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following the CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Intervention

This section is applicable to participants with liver involvement who meet PHL criteria on study intervention, having previously met PHL criteria at a study visit prior to starting study intervention.

At the first on-study intervention occurrence of PHL criteria being met the investigator will determine if there has been a **significant change** in the participants' condition compared with the last visit where PHL criteria were met.

- If there is no significant change no action is required.
- If there is a significant change, notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process.

Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a participant meets PHL criteria on study intervention and has already met PHL criteria at a previous on-study intervention visit.

The requirement to conduct Follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL and answer the following question:

Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study (eg, chronic or progressing malignant disease, severe infection, or liver disease)?

- **If No:**
Follow the process described in "Potential Hy's Law Criteria Met" for reporting PHL as an SAE.
- **If Yes:**
Determine if there has been a significant change in the participant's condition compared with when PHL criteria were previously met.

A "significant" change in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) in isolation or in combination or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator; this may be in consultation with the study physician if there is any uncertainty.

Hy's Law Lab Kit for Central Laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV HBsAg IgM and IgG anti-HBc HBV DNA ^a IgG anti-HCV HCV RNA ^b IgM anti-HEV HEV RNA
Other viral infections	IgM and IgG anti-CMV IgM and IgG anti-HSV IgM and IgG anti-EBV
Alcoholic hepatitis	CD-transferrin ^c
Autoimmune hepatitis	ANA Anti-LKM Ab ASMA
Metabolic diseases	Alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin ^c Transferrin saturation

^a HBV DNA is only recommended when IgG anti-HBc is positive.

^b HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive.

^c CD-transferrin and transferrin are not available in China. Study teams should amend this list accordingly.

Ab = antibody; ANA = antinuclear antibody; anti-HBc = hepatitis B core antibody; ASMA = anti-smooth muscle Ab; CD-transferrin=carbohydrate deficient transferrin; CMV = cytomegalovirus; DNA = deoxyribonucleic acid; EBV = Epstein-Barr virus; GGT = gamma-glutamyl transferase; HAV = hepatitis A virus; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HEV = hepatitis E virus; HSV = herpes simplex virus; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; LKM = liver/kidney microsomal antibody; RNA = ribonucleic acid.

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Appendix E Known Inhibitors or Inducers of CYP3A

Strong Inhibitors of CYP3A ^c	Moderate Inhibitors of CYP3A ^c
Boceprevir	Aprepitant
Clarithromycin ^a	Cimetidine
Cobicistat ^a	Ciprofloxacin
Conivaptan ^a	Clotrimazole
danoprevir and ritonavir ^b	crizotinib
Diltiazem ^a	Cyclosporine
elvitegravir and ritonavir ^b	Dronedarone ^a
grapefruit juice ^d	Erythromycin
Idelalisib	Fluconazole
indinavir and ritonavir ^b	Fluvoxamine
Itraconazole ^a	Imatinib
ketoconazole	Tofisopam
lopinavir and ritonavir ^{a b}	Verapamil ^a
Nefazodone	
Nelfinavir ^a	
paritaprevir and ritonavir and (ombitasvir and/or dasabuvir) ^b	
posaconazole	
Ritonavira ^b	
saquinavir and ritonavir ^{a b}	
Telaprevir ^a	
tipranavir and ritonavir ^{a b}	
troleandomycin	
voriconazole	

^a Inhibitor of P-glycoprotein.

^b Ritonavir is usually given in combination with other anti-HIV or anti-HCV drugs in clinical practice. Caution should be used when extrapolating the observed effect of ritonavir alone to the effect of combination regimens on CYP3A activities.

^c After discontinuation of the strong or moderate CYP3A inhibitor, wait 3 days before resuming acalabrutinib.

^d The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent.

CYP = cytochrome P450; HCV = hepatitis C virus; HIV = human immunodeficiency virus.

Strong Inducers of CYP3A	Moderate Inducers of CYP3A
carbamazepine	Bosentan
enzalutamide	Efavirenz
mitotane	Etravirine
phenytoin	Modafinil
rifampin	
St John's wort ^a	

^a The effect of St John's wort varies widely and is preparation-dependent.

Note: The list of drugs in these tables is not exhaustive. Any questions about drugs not on this list should be addressed to the medical monitor of the protocol.

Source: FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors, and Inducers.

[Website] Accessed 24 July 2019.

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#inVivo>

CYP = cytochrome P450; FDA = Food and Drug Administration.

Appendix F Guidance and Definitions for Reproduction and Contraception

Guidance and Definitions

Women of childbearing potential must use a highly effective form of contraception while on the study and for 2 days after the last dose of acalabrutinib.

Contraception measures and restrictions on sperm donation are not required for male participants.

Participants in clinical studies should promptly notify the investigator if they or their partner become pregnant during the study or within 2 days after the last dose of acalabrutinib. If a female participant becomes pregnant during the treatment period, she must discontinue acalabrutinib. Pregnancy in a female participant or a male participant's partner must be reported.

Definitions for WOCBP and for Participants of Non-reproductive Potential

Women of childbearing potential are women who are fertile following menarche and until becoming postmenopausal unless permanently sterile; permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

Women are considered to be of non-reproductive potential if they meet any of the following criteria:

- Postmenopausal, defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age, a high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation/occlusion, at least 6 weeks before screening.
- Have a congenital or acquired condition that prevents childbearing.

Men are considered to be of non-reproductive potential if they are permanently sterile due to bilateral orchidectomy.

Definition for Highly Effective Methods of Contraception

Highly effective methods of contraception (to be used during heterosexual activity) are defined as methods that can achieve a failure rate of < 1% per year when used consistently and correctly. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, which may be oral, intravaginal, or transdermal.
- Progestogen-only hormonal contraception associated with inhibition of ovulation, which may be oral, injectable, or implantable.
- Intrauterine device or intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Vasectomy of a female participant's male partner (with medical assessment and confirmation of vasectomy surgical success).
- Sexual abstinence (only if refraining from heterosexual intercourse during the entire period of risk associated with the study interventions).

Hormonal contraception may be susceptible to interaction with study or other drugs, which may reduce the efficacy of the contraception method.

Abstinence (relative to heterosexual activity) can only be used as the sole method of contraception if it is consistently employed during the entire period of risk associated with the study interventions as the participant's preferred and usual lifestyle. Periodic abstinence (eg, calendar, ovulation, sympto-thermal, and post-ovulation methods) and withdrawal are not acceptable methods of contraception.

If a contraceptive method is restricted by local regulations/guidelines, then it does not qualify as an acceptable highly effective method of contraception for participants participating at sites in the relevant country/region.

Appendix G Cumulative Illness Rating Scale

The Modified Cumulative Illness Rating Scale

Please take into account that CLL induced illness or organ damage are not included in this rating scale.

Body system	Score				
1. Cardiac (heart only)	0	1	2	3	4
2. Hypertension (rating is based on severity; organ damage is rated separately)	0	1	2	3	4
3. Vascular (blood, blood vessels and cells, bone marrow, spleen, lymphatics)	0	1	2	3	4
4. Respiratory (lungs, bronchi, trachea below the larynx)	0	1	2	3	4
5. EENT (eye, ear, nose, throat, larynx)	0	1	2	3	4
6. Upper GI (esophagus, stomach, and duodenum; pancreas; do not include diabetes)	0	1	2	3	4
7. Lower GI (intestines, hernias)	0	1	2	3	4
8. Hepatic (liver and biliary tree)	0	1	2	3	4
9. Renal (kidneys only)	0	1	2	3	4
10. Other genitourinary (ureters, bladder, urethra, prostate, genitals)	0	1	2	3	4
11. Muscular-skeletal-integumentary (muscle, bone, skin)	0	1	2	3	4
12. Neurological (brain, spinal cord, nerves, do not include dementia)	0	1	2	3	4
13. Endocrine-metabolic (includes diabetes, thyroid; breast; systemic infections; toxicity)	0	1	2	3	4
14. Psychiatric/Behavioral (includes dementia, depression, anxiety, agitation/delirium, psychosis)	0	1	2	3	4

EENT = eyes, ears, nose, and throat; GI = gastrointestinal

RATING SUGGESTIONS (GENERAL PRINCIPLES)

Every single disease must be classified in the appropriate system. If there are several problems in the same system, only the most severe is rated. Example: for a participant suffering from a well-controlled angina (Rated 2) and terminal heart failure (Rated 4), only the higher rated condition would be scored in the cardiac system (eg, rating is 4).

The spread of a cancer may lead to rate the condition in more than 1 category. For example, a lung cancer with bone metastases treated with NSAIDs is rated 4 in respiratory and 2 in musculoskeletal.

General rules for severity rating:

0. No problem affecting that system or past problem without clinical relevance.
1. Current mild problem or past significant problem.
2. Moderate disability or morbidity and/or requires first-line therapy.
3. Severe problem and/or constant and significant disability and/or hard to control chronic problems (complex therapeutic regimen).
4. Extremely severe problem and/or immediate treatment required and/or organ failure and/or severe functional impairment.

LEVEL 0

No problem or healed minor injuries; past childhood illnesses (chickenpox); minor surgery (carpal tunnel completely healed, Cesarean); uncomplicated healed fractures; other past problems healed without sequel, residual, or complication (pneumonia).

LEVEL 1

Any current medical problem that causes mild discomfort or disability, or has occasional exacerbations, having only minor effect on morbidity (asthma controlled with bronchodilators, occasional heartburn relieved with antacids). Medical problems that are not currently active but were significant problems in the past (passage of a kidney stone) or required major surgery (hysterectomy, cholecystectomy, appendectomy).

LEVEL 2

Medical conditions that require daily treatment or first-line therapy (asthma controlled with inhaled steroids, gastroesophageal reflux treated with daily medication, osteoarthritis requiring daily NSAID, etc.) and/or have moderate disability or morbidity.

LEVEL 3

Chronic conditions that are not controlled with first-line therapy (asthma needing continuous corticosteroid therapy, symptomatic angina despite medical regimes, heart failure with symptoms or uncontrolled hypertension despite complex therapeutic regimen) and/or constant significant disability, but not severe disability.

LEVEL 4

Any acute condition that requires immediate treatment or hospitalization (unstable angina, acute myocardial infarction, stroke, but also bladder outlet obstruction) and/or extremely severe problems; organ failure (end-stage renal disease needing dialysis, oxygen-dependent COPD, terminal heart failure); severe sensory impairment (almost complete blindness or deafness, being wheelchair bound) and/or severely affected quality of life, severe impairment in function; delirium by medical (organic) conditions.

RATING MALIGNANCIES

Consistent scoring of severity ratings for various malignancies is a difficult problem. Each malignancy has its own rating system and prognostic indicators, the complexity of which would quickly exceed the aim of the intended simplicity and ease of use of CIRS.

The following general guidelines are intended to provide a reasonably accurate delineation of medical burden for cancer without excessive complexity.

Level 1: Cancer diagnosed in the remote past without evidence of recurrence or sequel in the past 10 years or skin cancer excised in the past without major sequel (other than melanoma).

Level 2: No evidence of recurrence or sequel in the past 5 years.

Level 3: Required chemotherapy, radiation, hormonal therapy or surgical procedure for cancer in the past 5 years.

Level 4: Recurrent malignancy or metastasis (other than to lymph glands) or palliative treatment stage.

These ratings are to be made in the appropriate organ category for a given malignancy.

ORGAN-SPECIFIC CATEGORIES

The following organ-specific categories will attempt to provide guidelines for consistent rating of comparable severity. Common conditions will be stressed with the focus on the “judgment strategy” that can be applied to other problems not listed.

If there are several problems in the same system, only the most severe is rated.

HEART

In this category, only heart and coronary disease have to be considered (not vascular): coronary arteries disease, heart failure, valvular heart diseases, heart disease secondary to hypertension, endocarditis, myocarditis, pericarditis, arrhythmias (extrasystoles, bundle-branch blocks, atrial fibrillation, pacemaker placement), heart malignancies. Functional impact must be considered too (eg, NYHA II heart failure has different value between dependent and independent persons).

0. No problems
1. Remote myocardial infarction (> 5 years ago); occasional [exertion] angina; asymptomatic valvular disease
2. Congestive heart failure compensated with meds (NYHA I-II); daily anti-angina meds; left ventricular hypertrophy; atrial fibrillation, bundle-branch block, daily anti-arrhythmic drugs (even for prophylaxis); pacemaker placement for asymptomatic bradycardia; valvular disease requiring medical treatment
3. Previous myocardial infarction (< 5 years ago); abnormal stress test; status post (previous) percutaneous coronary angioplasty, coronary artery bypass graft surgery or other cardiac surgery (valve replacement); moderate CHF (NYHA II-III) or complex medical treatment; bifascicular block; pacemaker placement for cardiogenic syncope; pericardial effusion or pericarditis
4. Acute coronary syndrome, unstable angina or acute MI; intractable CHF (NYHA III-IV acute or chronic); marked restriction to the normal activity of daily living secondary to cardiac status

HYPERTENSION

Consider only hypertension severity; organ damage (complications) should be considered into the respective categories.

0. Normotension
1. Borderline hypertension; hypertension compensated with salt restriction and weight loss, drug free (when drug therapy is indicated, but the participant does not take meds, the score is at least 2)
2. Daily antihypertensive meds: hypertension controlled by 1 pill therapy (even fixed doses combinations)
3. Hypertension requiring 2 or more pills for control
4. Malignant hypertension, or hypertension non-controlled by complex therapeutic regimen

VASCULAR-HEMATOPOIETIC

Artery disease: carotid atherosclerosis, PAD, aneurysms (every site);

Venous disease: venous insufficiency, varices, DVT, pulmonary embolism, primary pulmonary hypertension;

Immunologic disease: systemic lupus erythematosus, systemic sclerosis (scleroderma), sarcoidosis, hypersensitivity.

0. No problem
1. Venous insufficiency, varices, lymphedema; carotid stenosis < 70%; hemoglobin 10 to 12 g/dL (in females), 12 to 14 g/dL (in males); anemia of chronic “inflammatory” disease
2. Previous DVT; 1 symptom of atherosclerosis disease (claudication, bruit, amaurosis fugax, absent pedal pulses) or daily meds (eg, anti-platelets drugs); PAD IIa-IIb by Fontaine; carotid stenosis > 70%; aortic aneurysm < 4 cm; hemoglobin 8 to 10 g/dL (in females), 10 to 12 g/dL (in males); anemia secondary to iron, B12 vitamin or folate deficiency, or to chronic renal failure; total WBC 2000 to 4000/mm³; mild thrombocytopenia (50000 to 150000/mm³)
3. Deep venous thrombosis or recent DVT (< 6 months ago); 2 or more symptoms of atherosclerosis (see above); PAD Fontaine III or recent/previous angioplasty (with or without stenting); hemoglobin < 8 g/dL (in females), < 10 g/dL (in males); dyserythropoietic anemia; WBC < 2000/mm³; severe thrombocytopenia (< 50000/mm³)
4. Pulmonary embolism (acute or recent/previous); atherosclerosis requiring surgical intervention (eg, aortic aneurysm > 4 cm, symptomatic carotid stenosis > 70%, PAD Fontaine IV or amputation for vascular causes, etc.); recent/previous vascular surgery; any hematological or vascular malignancy (including multiple myeloma)

In case of immunological disease, score should be assigned by considering blood abnormalities, stadium of organ damage and/or functional disability (2: symptoms controlled by daily meds; 3: symptoms not well controlled; 4: symptoms impossible to be controlled or short time poor prognosis).

RESPIRATORY

In this category COPD, asthma, emphysema, restrictive pulmonary interstitial lung diseases, malignancies of lung and pleura, pneumonia, and smoking status are considered.

0. No problem
1. Recurrent episodes of acute bronchitis; currently treated asthma with as needed (prn) inhalers when required; cigarette smoker > 10 but < 20 pack-years
2. Instrumental diagnosis of COPD or pulmonary interstitial disease (x-ray, CT, spirometry); daily prn inhalers (≤ 2 pharmacological classes); 2 or more episodes of pneumonia in the last 5 years; cigarette smoker > 20 but < 40 pack-years
3. Exertion dyspnea secondary to limited respiratory capacity, not well controlled by daily meds; required oral steroids for lung disease; daily prn inhalers (3 pharmacological classes); acute pneumonia treated as an outpatient
4. Chronic supplementation of oxygen; respiratory failure requiring assisted ventilation, or previous (at least 1 episode); any lung or pleural neoplasm; acute pneumonia requiring hospitalization

Smoking is an important respiratory and cardiovascular risk, so it is considered as a disease, and it is rated according to lifetime pack-years:

Number of cigarette packs smoked per day $\times$ Number of years smoked in their lifetime
eg, 1 pack-year = 20 cigarettes/day (1 pack) $\times$ 1 year

Ex-smokers should be rated too, but those who have been smoke-free for the most recent 20 years would merit a lower rating than those who are currently smoking.

Examples:

- (a) Participant smoking 20 cig/day (1 pack) for 25 years = 25 pack-years – CIRS score: 2
- (b) Participant smoking 40 cig/day (2 packs) for 25 years = 50 pack-years – CIRS score: 3
- (c) Ex-smoker of 20 cig/day (1 pack) for 25 years, stopped 5 years ago – CIRS score: 2
- (d) Ex-smoker of 20 cig/day (1 pack) for 25 years, stopped 20 years ago – CIRS score: 1

Classification of COPD could be more specific when instrumental data (objective evidence) are available: blood gas, forced expiratory volume in 1 second, etc.

EYES, EARS, NOSE and THROAT, and LARYNX

To simplify the potential complexity of this category it was decided to score according to the severity of the disability created by sensory diseases (degree of limited autonomy and

communication), and avoid rating each type of pathology. Sensory impairments should be rated after instrumental correction (corrective lenses, hearing aid, etc.).

Eyes: glaucoma, cataracts, macular degeneration (diabetic/hypertensive retinopathy), any other pathology

Ears: otitis, dizziness, any cause of hearing impairment

Nose and Throat: rhinitis, pharyngitis, nasal polyps, sinusitis, malignancies

Larynx: dysphonia, acute and chronic laryngitis, malignancies

0. No problems
1. Corrected vision with glasses; mild hearing loss; chronic sinusitis
2. Difficulty in reading newspaper or drive although glasses; required hearing aid; chronic sinonasal complaints requiring medication; vertigo/dizziness requiring daily medications
3. Severe low vision, partially blind (required an escort to venture out, unable to read newspaper); severe ear impairment (conversational hearing still impaired with hearing aid); laryngeal dysphonia (not neurological dysarthria)
4. Functional blindness/deafness: unable to read, recognize a familiar face, unable to conversational hearing, even if “organically” he is not completely blind or deaf; laryngectomy (every cause, especially malignancies); required surgical intervention for vertigo; aphonia secondary to laryngeal impairment

UPPER GASTROINTESTINAL SYSTEM

This category is comprehensive of the intestinal tract from esophagus to duodenum, and pancreatic trees: dysphagia, GERD, hiatal hernia, esophageal diverticula, any type of gastritis (consider also H. pylori eradication or not), gastric/duodenal ulcer, acute or chronic pancreatitis, malignancies (comprehensive of gastric lymphoma).

Ensure that type 1 diabetes is rated under “metabolic.”

0. No problem
1. Hiatal hernia, GERD or gastritis requiring meds; previous ulcer (> 5 years ago); previous *Helicobacter pylori* eradication therapy (> 5 years ago)
2. Daily proton-pump inhibitor/antacid meds; documented gastric or duodenal ulcer or H. pylori eradication therapy within 5 years
3. Active gastric or duodenal ulcer; positive fecal occult blood test; any swallowing disorder or dysphagia; chronic pancreatitis requiring supplemental pancreatic enzymes for digestion; previous episode of acute pancreatitis

4. Any type of malignancies (see “Rating Malignancies”); previous gastric surgery because of cancer; history of perforated ulcer (gastric surgery not because of cancer, cecorrhaphy); melena/heavy bleeding from upper GI source; acute pancreatitis

LOWER GASTROINTESTINAL SYSTEM

Comprehensive of the rest of the GI system, from small bowel to anus: Whipple’s disease, diverticulosis, irritable bowel, malignancies. Constipation is rated, too, by type and frequency of laxatives required, or by history of impaction.

0. No problems, previous appendectomy, previous hernia repair (without complications)
1. Constipation managed with meds; active hemorrhoids; intestinal hernia requiring surgery; previous hernia repair with complications (intestinal adhesions, laparocoele, etc.); irritable bowel syndrome (few symptoms)
2. Constipation requiring daily bulk laxatives (psyllium, polycarbophil, sterculia, guar gum, etc.), or stool softeners; diverticulosis (previous diverticulitis); inflammatory bowel disease in remission with meds (> 5 years ago)
3. Bowel impaction/diverticulitis within the last year; daily use of stimulant (irritant) or osmotic laxatives (bisacodyl, senna, glycerol, sodium docusate; lactulose, polyethylene glycol) or enemas; chronic bowel inflammation in remission with meds (< 5 years ago)
4. Diverticulitis flare up; active inflammatory disease; current impaction; hematochezia/active bleeding from lower GI source; bowel carcinoma

LIVER AND BILIARY TREES

Comprehensive of liver, gallbladder, biliary trees, portal system: acute and chronic hepatitis (viral, alcoholic, toxic, autoimmune, idiopathic), cirrhosis, portal hypertension, hemochromatosis, primary biliary cirrhosis, cholelithiasis, cholangitis, primary malignancies. As the hepato-biliary system is difficult to assess through the physical examination, therefore, laboratory results must be used.

0. No problem
1. History of hepatitis (actually normal values of transaminases); cholecystectomy
2. Cholelithiasis; chronic hepatitis or previous hepatitis (< 5 years ago) or any other liver disease (hemochromatosis, primary biliary cirrhosis) with mildly elevated transaminases (within 3 times normal values); heavy alcohol use within 5 years (to rate in “psychiatric”, too)
3. Chronic hepatitis or any other liver disease with marked elevation of transaminases (> 3 times normal values); elevated bilirubin
4. Acute cholecystitis; any biliary obstruction; active hepatitis/liver cirrhosis; any liver or biliary tree carcinoma

RENAL

This category is exclusive of kidney: kidney stones, acute/chronic renal failure, glomerulonephritis; nephrosic/nephritic syndrome; active/chronic pyelonephritis, diabetic or hypertensive nephropathy (albuminuria/proteinuria), renal carcinoma. Bence Jones proteinuria in multiple myeloma should not be considered.

0. No problem
1. Asymptomatic kidney stone; kidney stone passage within the last 10 years; pyelonephritis within 5 years; kidney cysts without hematuria
2. Serum creatinine > 1.5 but < 3 mg/dL without diuretic or antihypertensive medication (particularly angiotensin converting enzyme inhibitors or renin-angiotensin-aldosterone system blockers); kidney calculi requiring daily meds
3. Serum creatinine > 3 mg/dL or < 1.5 mg/dL in conjunction with diuretics, antihypertensive, or bicarbonate therapy; active pyelonephritis; nephrosic syndrome; colic symptoms treated as an outpatient
4. Required dialysis; renal carcinoma; colic symptoms requiring hospitalization

GENITOURINARY

Ureters, bladder, urethra. Genitals, prostate, testicles, penis, seminal vesicles.

Uterus, ovaries. Mammary gland is rated under “metabolic”.

This category is comprehensive of all genitourinary-tract impairments: ureteral or bladder stones, BPH, UTIs, prolapses, etc. Urinary incontinence and indwelling catheter should also be considered.

0. No problem
1. Stress incontinence; BPH without urinary symptoms; hysterectomy or ovariectomy (uterine fibroma, benign neoplasm)
2. Pathological pap smear (or 2 consecutives abnormal); frequent UTIs (3 or more in the past year) in female or current UTIs; urinary incontinence (not stress) in females; BPH with urinary symptoms (frequency, urgency, hesitancy); status post-TURP; any urinary diversion procedure; indwelling catheter; bladder calculi
3. Prostatic cancer in situ (eg, incidentally found during TURP); vaginal bleeding; cervical carcinoma in situ; hematuria (any cause); urinary incontinence (not stress) in males; bladder polyps
4. Acute urinary retention; current urosepsis; any genitourinary malignancies except as above

MUSCULOSKELETAL/INTEGUMENT

This is a very broad category, including: osteoarthritis, osteoporosis, any bone fracture; primary neoplasm (bone, muscle, connective tissue, skin), distinguishing melanoma from other localized skin cancers; rheumatoid arthritis and polymyalgia rheumatica; muscular injuries (rotator cuff, long head of the biceps); pressure sores; any dermatological disease.

The scores of this category are strictly correlated to the disability they cause; for the evaluation of the level of disability, refer to BADL and IADL.

NOTICE: score the severity of each illness according to the level of disability caused by the same illness in this category, without considering the disability caused by other diseases. For example, a participant affected both by osteoarthritis and hemiplegia from a previous stroke has a high level of disability, but you have to score 2 for disability by osteoarthritis (in this category) and 4 for disability by stroke (in the neurological category); for a participant with both a deforming rheumatoid arthritis and a previous stroke without remaining outcomes you have to score 4 for disability from arthritis (in this category) and 2 for disability from stroke (in the neurological category).

0. No problem
1. Requires meds for osteoarthritis (NSAID) or has mildly limited IADL from joint pathology; excised skin cancers (except melanoma); skin infections requiring antibiotics within a year
2. Daily anti-osteoarthritis meds (NSAID) or use of assistive devices or little limitation in ADL (previous arthroprosthesis or treated fracture with a low level of remaining disability); osteoporosis without vertebral fractures; daily meds for chronic skin diseases (even local, as psoriasis or pressure sores); non-metastatic melanoma; daily meds for rheumatoid arthritis (except steroids) with a low level of disability
3. Osteoarthritis with a moderate level of disability in ADL; requires chronic treatment with steroids for arthritic conditions or joints' deformities or severely impaired; osteoporosis with vertebral compression fractures
4. Wheelchair bound for osteomuscular disease; severe joint deformities or severely impaired usage; osteomyelitis; any bone or muscle or connective tissue neoplasm (see "Rating Malignancies"); metastatic melanoma

Fractures and/or arthroprosthesis (both recent and old) have to be scored according to the level of disability they cause (considering outcomes too), to avoid confusion about possible classifications of different fractures or joints. The same is true for muscular diseases.

CENTRAL AND PERIPHERAL NERVOUS SYSTEM

This category includes the “somatic” pathologies of the central and peripheral nervous system: any kind of stroke, neurodegenerative diseases (Parkinson’s disease and parkinsonism, multiple sclerosis, amyotrophic lateral sclerosis, etc.), myelopathies, traumas with neurological outcomes, primary or secondary epilepsy, neuropathies (diabetic, alcoholic, any other etiology), primary tumors, chronic headaches (migraine), insomnia, etc. It must carefully estimate the severity and prognosis of the illness but also the functional impairment that the illness causes.

0. No problem (or fewer convulsions in childhood)
1. Frequent headaches requiring meds without impairment in advanced ADL; previous TIA (1 event); previous epilepsy, actually not treated, without crisis since more than 10 years ago
2. Chronic headache requiring daily meds (even for prophylaxis) or with regularly functional impairment in advanced ADL (bed rest, job withdrawal, etc.); actual TIA or more than 1 previous TIA; previous stroke without significant residual; mild severity neurodegenerative diseases (see above), treated and well controlled; epilepsy controlled with drugs
3. Previous stroke with mild residual dysfunction (hemiparesis, dysarthria); any neurosurgical procedure; moderate severity neurodegenerative diseases (see above), not well controlled by meds; epilepsy in treatment but with periodic crisis
4. Acute stroke or previous stroke with severe residual dysfunction (hemiplegia, aphasia, severe vascular dementia) or more than 1 previous stroke (multi-infarct encephalopathy); severe neurodegenerative diseases (see above) causing disability in ADL; neurological coma

Alzheimer’s Disease and dementia should not be rated into this category (Psychiatric and behavioral diseases): Alzheimer’s Disease should be listed only under psychiatric disorders; if dementia stems from vascular and/or mixed dementia and/or other neurological condition (eg, Parkinson’s Disease), both “neurologic” and “psychiatric” categories should be endorsed at the appropriate level for severity, considering in this category the stroke and the multi-infarct encephalopathy responsible for the cognitive impairment (score 3 for stroke with remaining outcomes, score 4 for multi-infarct encephalopathy).

ENDOCRINE-METABOLIC SYSTEM AND BREAST (systemic infections and poisonings)

Type 1 and Type 2 diabetes (organ damage should be considered into the respective categories, like for hypertension), obesity and dyslipidemia (hypercholesterolemia) represent the core of this category; it also includes hypo- and hyperthyroidism, hypo- and hyper-parathyroidism, adrenal pathologies (Cushing' or Addison' Disease), hypogonadism, hypopituitarism, etc. Malignancies of these glands, both benignant (like thyroid nodules) and malignant (like thyroid or adrenal cancer, vipoma, etc.) are included too.

Even if it is an exocrine gland, breast was included in this category because the authors did not find a more appropriate one; so it also includes breast cancer.

Moreover, it includes electrolyte disorders, sepsis, systemic infections (like tuberculosis, syphilis, AIDS) scored according to their severity and the functional impairment they cause (see general indications) and poisonings (chronic by metals or acute by pesticides or carbon monoxide).

0. No problem
1. Diabetes and/or dyslipidemia compensated with diet; mild obesity (BMI 30 to 35 kg/m²); hypothyroidism in replacement therapy (L-thyroxin); hyperthyroidism caused by Plummer' adenoma surgically treated
2. Diabetes compensated with oral hypoglycemic drugs or insulin (hemoglobin A1c < 7%); dyslipidemia well controlled by daily meds (c-LDL lower than the recommended target according to the individual global cardiovascular risk); moderate obesity (BMI 35 to 45 kg/m²); hyperthyroidism in pharmacologic treatment; asymptomatic or surgically treated hyperparathyroidism; fibrocystic breast disease
3. Diabetes not well compensated by therapy (hemoglobin A1c 7% to 8.5%, presence of complications); dyslipidemia not well controlled (c-LDL higher than the recommended target according to the individual global cardiovascular risk; for instance, c-LDL > 100 mg/dL in participants with previous myocardial infarction or stroke); severe obesity (BMI > 45 kg/m²); symptomatic hyperparathyroidism (eg, hypercalcemia); replacement therapy for adrenal failure; any electrolytes disorder requiring hospitalization
4. Uncontrolled diabetes (hemoglobin A1c > 8.5%) or 1 diabetic ketoacidosis or nonketotic hyperosmolar coma during the past year; genetic uncontrolled dyslipidemia; acute adrenal failure during hormonal replacement therapy; any neoplasm of thyroid, breast, adrenal gland (see "Rating Malignancies")

NOTICE: when the participant is not treated with drug therapy for diabetes or dyslipidemia but he should be for the optimal control of the pathology (for instance, hemoglobin A1c > 7%, total cholesterol > 250 mg/dL), score the pathology according to the laboratory values, which really define its severity.

PSYCHIATRIC AND BEHAVIORAL DISEASES

This category includes both dementia and related behavioral disorders (psychosis, anxiety, depression, agitation) and all the pre-existing and/or not related to dementia psychiatric disorders. Since this is the only item analyzing participant's mental status (all the others refer to physical status), it is very important to evaluate it carefully considering further information derived from the Comprehensive Geriatric Assessment (MMSE; GDS, Neuro-Psychiatric Inventory if available).

0. No psychiatric problem or history thereof.
1. Minor psychiatric condition or history thereof: previous (occasional) psychiatric treatment without hospitalization; major depressive event and/or use of antidepressants more than 10 years ago without hospitalization; occasional use of minor tranquilizers (eg, benzodiazepine; even if as hypnotherapy for insomnia); mild cognitive impairment (MMSE 25 to 28).
2. A history of major depression (according to DSM-IV criteria) within the last 10 years (treated or untreated); mild dementia (MMSE 20 to 25); previous admission to Psychiatric Department for any reason; history of substance abuse (more than 10 years ago, including alcoholism).
3. Current major depression (according to DSM-IV criteria) or more than 2 previous major depression episodes in the past 10 years; moderate dementia (MMSE 15 to 20); current and usual usage of daily anti-anxiety meds (even as hypnotherapy for insomnia); current or within the past 10 years substance abuse or dependence (according to DSM-IV criteria); requires daily antipsychotic medication; previous attempt at suicide.
4. Current mental illness requiring psychiatric hospitalization, institutionalization, or intensive outpatient management (psychiatric emergency, as attempt at suicide or severe depression with suicide purpose, acute psychosis or acute decompensation of chronic psychosis, severe substance abuse; severe agitation from dementia); severe dementia (MMSE < 15); delirium (acute confusion or altered mental status for medical (organic) reasons: in this case you have to codify also the medical cause in its own category with the appropriate level of severity).

A psychiatric consult could be requested for this category; dementia and depression, the most frequent diseases in the elderly, can be scored in detail using the MMSE and GDS. The severity of any mental disorder (dementia, depression, anxiety, psychosis, substance abuse and all the others) must be scored according to the level of functional impairment or disability they cause.

CHECKLIST

Medical History

- Timing of events and/or interventions (how long ago underwent surgery for...; how long ago had myocardial infarction or stroke, etc.) and evaluation of functional impairment.
- Drugs list (fundamental), including laxatives and tranquilizers (even hypnoinducents).
- Symptoms of atherosclerotic disease (TIA, angina, claudication, amaurosis).
- Etiological diagnosis (reasonably reliable) of anemia.
- Degree of vascular stenosis or aneurism dimension (by Doppler and/or ultrasound and/or CT data, when available).
- Information about smoking status (how many cigarettes per day for how many years, when stopped).
- Use of glasses? With this aid, the participant is able to read a newspaper? Requires an escort to venture out?
- Any hearing aid? (you should evaluate possibility to communicate with participant).
- “Peptic history” of the participant (including previous eradication therapy for *H. pylori*).
- Urinary symptoms, incontinence, presence of bladder catheter (even from BADL).

Physical Examination

- Height (m²) and weight (kg) (measured, not reported, if possible) to calculate BMI
- Blood pressure, heart rate, cardiac murmurs, peripheral arterial pulses
- Joint pain or passive stiffness limitation (non-x-ray-based diagnosis of osteoarthritis)
- Residual neurological deficits (dysarthria/aphasia, hemiparesis/hemiplegia)

Baseline Laboratory Samples

- Blood count: hemoglobin, WBC, and platelet count
- Creatinine, electrolytes
- AST, ALT, fractionated bilirubin
- Thyroid function and serum B12 (when indicated)
- Hemoglobin A_{1c} (for diabetic participants)

Source: [Extermann et al. 1998](#)

Appendix H Response Assessment Criteria (Modified from Hallek et al. 2018)

Response Definition After Treatment for CLL Patients

Group	Parameter	CR	PR	PD	SD
A	Lymph nodes	None ≥ 1.5 cm	Decrease $\geq 50\%$ (from baseline)*	Increase $\geq 50\%$ from baseline or from response	Change of -49% to $+49\%$
	Liver and/or spleen size†	Spleen size < 13 cm; liver size normal	Decrease $\geq 50\%$ (from baseline)	Increase $\geq 50\%$ from baseline or from response	Change of -49% to $+49\%$
	Constitutional symptoms	None	Any	Any	Any
	Circulating lymphocyte count	Normal	Decrease $\geq 50\%$ from baseline	Increase $\geq 50\%$ over baseline	Change of -49% to $+49\%$
B	Platelet count	$\geq 100 \times 10^9/L$	$\geq 100 \times 10^9/L$ or increase $\geq 50\%$ over baseline	Decrease of $\geq 50\%$ from baseline secondary to CLL	Change of -49 to $+49\%$
	Hemoglobin	≥ 11.0 g/dL (untransfused and without erythropoietin)	≥ 11 g/dL or increase $\geq 50\%$ over baseline	Decrease of ≥ 2 g/dL from baseline secondary to CLL	Increase < 11.0 g/dL or $< 50\%$ over baseline, or decrease < 2 g/dL
	Marrow	Normocellular, no CLL cells, no B-lymphoid nodules	Presence of CLL cells, or of B-lymphoid nodules, or not done	Increase of CLL cells by $\geq 50\%$ on successive biopsies	No change in marrow infiltrate

*Sum of the products of 6 or fewer lymph nodes (as evaluated by CT scans and physical examination in clinical trials or by physical examination in general practice).

†Spleen size is considered normal if < 13 cm. There is not firmly established international consensus of the size of a normal liver; therefore, liver size should be evaluated by imaging and manual palpation in clinical trials and be recorded according to the definition used in a study protocol.

CR, complete remission (all of the criteria have to be met); PD, progressive disease (at least 1 of the criteria of group A or group B has to be met); PR, partial remission (for a PR, at least 2 of the parameters of group A and 1 parameter of group B need to improve if previously abnormal; if only 1 parameter of both groups A and B is abnormal before therapy, only 1 needs to improve); SD, stable disease (all of the criteria have to be met; constitutional symptoms alone do not define PD).

CLL = chronic lymphocytic leukemia; CR = complete response; CT = computed tomography; PD = progressive disease; PR = partial response; SD = stable disease.

Constitutional symptoms include the following:

- Unintentional weight loss $\geq 10\%$ within the previous 6 months.
- Significant fatigue (ie, ECOG performance scale 2 or worse; cannot work or unable to perform usual activities).
- Fevers $\geq 100.5^{\circ}\text{F}$ or 38.0°C for 2 or more weeks without evidence of infection.
- Night sweats for ≥ 1 month without evidence of infection.

Complete Response

Complete response requires all of the following criteria:

- Peripheral blood lymphocytes (evaluated by blood and differential count) $< 4 \times 10^9/\text{L}$.
- Absence of significant lymphadenopathy by physical examination. In clinical trials, a CT scan of the neck, abdomen, pelvis, and thorax is desirable if previously abnormal. Lymph nodes should be < 1.5 cm in longest diameter. Once this is determined, further imaging should not be required until disease progression is apparent by clinical examination or on blood testing.
- No splenomegaly or hepatomegaly by physical examination. In clinical trials, a CT scan of the abdomen should be performed at response assessment and should show no evidence for lymphadenopathy and splenomegaly. We propose to use a recent consensus response cutoff for splenomegaly of 13 cm in craniocaudal length. However, the persistence of splenomegaly may not correlate with outcome. The quantitative determination of hepatomegaly seems more difficult; changes such as focal or disseminated hepatic nodules support liver involvement.
- Absence of disease-related constitutional symptoms.
- Blood counts need to show the following values:
 - Neutrophils $\geq 1.5 \times 10^9/\text{L}$.
 - Platelets $\geq 100 \times 10^9/\text{L}$.
 - Hemoglobin ≥ 11.0 g/dL (without red blood cell transfusions).
- MRD assessment. In clinical trials aimed at maximizing the depth of remission, the presence of MRD after therapy should be assessed. The sensitivity of the method used to evaluate for MRD should be reported, as should the tissue studied (blood or marrow).
- For participants in clinical trials. A BM aspirate and biopsy should be performed if clinical and laboratory results for PB lymphocytes and blood counts (noted in above bullets) demonstrate that a CR may have been achieved. To define a CR, the cytological or pathological evaluation of the BM smear or biopsy must be at least normocellular for age, without evidence for typical CLL lymphocytes by morphological criteria. This evaluation is not based on a flow cytometry-based MRD assessment.

Complete Response with Incomplete Marrow Recovery

Some participants fulfill all the criteria for a CR (including the marrow examinations) but have a persistent anemia, thrombocytopenia, or neutropenia apparently unrelated to CLL, but related to drug toxicity. These participants should be considered as a different category of

remission, CRi. For the definition of this category, the marrow evaluation should be performed with scrutiny and not show any clonal disease infiltrate. In clinical trials, participants having CRi should be monitored prospectively to determine whether their outcome differs from that of participants with detectable residual disease or with noncytopenic CR.

Partial Response

To define a PR, at least 2 parameters of group A and 1 parameter of group B need to improve, if previously abnormal. If only 1 parameter of both groups A and B was abnormal before therapy, only 1 needs to improve ([Appendix Table I1](#)). Constitutional symptoms persisting for > 1 month should be recorded.

- A decrease in the number of blood lymphocytes to 50% or less from the value before therapy.
 - Reduction in lymphadenopathy compared with baseline (by cross-sectional imaging scans in clinical trials or by palpation in general practice) as defined by:
 - A decrease in LN size by 50% or more in the sum of the products of the same enlarged LNs selected at baseline as assessed by imaging (an established number in clinical trials of LNs has been up to 6)
- AND
- The sum of longest diameters of the same enlarged LNs selected at baseline as assessed by physical examination (an established number in clinical trials of LNs has been a maximum of 6)
 - No increase in any LN and no new enlarged LN (diameter ≥ 1.5 cm). For small LNs (longest diameter < 1.5 cm), an increase < 25% is not considered significant.
 - A regression $\geq 50\%$ of the extent of enlargement of the spleen below the costal margin defined by palpation, or normalization in size. When assessed by CT, scan spleen size must have regressed by $\geq 50\%$ in length beyond normal. A persistence of splenomegaly posttherapy may have limited influence on outcome in CLL.
 - A regression of $\geq 50\%$ of the extent of enlargement of the liver below the costal margin defined by palpation, or normalization in size. Given the impact of numerous medical conditions, liver size by physical examination or CT scan is not a reliable measure of hepatic involvement by CLL and should only be counted if hepatomegaly is clearly attributable to lymphoid involvement.
 - The blood count should show one of the following results:
 - Platelet counts $> 100 \times 10^9/\text{L}$ or 50% improvement over baseline.
 - Hb > 11.0 g/dL or 50% improvement over baseline without red blood cell transfusions or erythropoietin support.

Nodular Partial Remission

When performing marrow biopsies in clinical trials, lymphoid nodules can be found that may reflect residual disease. These nodules may be recorded as “nodular partial remission.”

Immunohistochemistry may be performed to define whether the nodules comprise primarily T cells, B cells other than CLL cells, or CLL cells. If nodules are not composed of CLL cells, a CR can be documented provided all other criteria are met. If the marrow is hypocellular, a repeat determination should be performed 4 weeks or later, when PB counts have recovered; however, this interval should not exceed 6 months after the last treatment. In cases in which a marrow biopsy was obtained at baseline, a comparison of pre- vs post-therapy biopsies should be performed.

Progressive Disease

Progressive disease during or after therapy is characterized by at least one of the following, when compared with nadir values:

- Lymphadenopathy. Progression of lymphadenopathy is often discovered by physical examination and should be recorded at regular intervals. In CLL, the use of imaging (CT scans) usually does not add much information for the detection of progression or relapse. Disease progression occurs if one of the following events is observed:
 - Appearance of any new lesion such as enlarged LNs (≥ 1.5 cm), splenomegaly, hepatomegaly, or other organ infiltrates. Transient increases of LN size during treatment with novel inhibitors may occur and should not be counted as PD.
 - An increase by $\geq 50\%$ in greatest determined diameter of any previous site (≥ 1.5 cm).
- An increase in the spleen size by $\geq 50\%$ or the de novo appearance of splenomegaly. In the setting of splenomegaly, the splenic length must increase by $\geq 50\%$ of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to ≥ 16 cm). If no prior splenomegaly was observed at baseline or if splenomegaly has resolved with treatment, the spleen must increase by at least 2 cm from baseline.
- An increase in the liver size of $\geq 50\%$ of the extent enlargement of the liver below the costal margin defined by palpation, or the de novo appearance of hepatomegaly. Given the impact of numerous medical conditions, liver size by physical examination or by CT scan is not a reliable measure of hepatic involvement by CLL and should only be counted if hepatomegaly is clearly attributable to lymphoid involvement.
- An increase in the number of blood lymphocytes by 50% or more with at least $5 \times 10^9/L$ B lymphocytes. Certain therapies (eg, kinase inhibitors) may cause lymphocytosis. In the setting of therapy with such agents, an increase in blood lymphocyte count by itself does not uniformly indicate an increased tumor burden, but may reflect redistribution of leukemia cells from lymphoid tissues to the blood. This should be pre-defined in the protocol of clinical trials for therapies in which redistribution of disease occurs. In such cases, increased lymphocytosis alone is not a sign of treatment failure or PD.

- Transformation to a more aggressive histology (Richter syndrome or Richter transformation). The diagnosis of Richter transformation should be established by LN or other tissue biopsy.
- Occurrence of cytopenia (neutropenia, anemia, or thrombocytopenia) directly attributable to CLL and unrelated to autoimmune cytopenias.

During therapy: Cytopenias may occur as a side effect of many therapies and should be assessed. During therapy, cytopenias cannot be used to define disease progression. Each protocol should define the amount of drug(s) to be administered with such cytopenias.

Post-treatment: The progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of Hb levels ≥ 2 g/dL or < 10 g/dL, or by a decrease of platelet counts $\geq 50\%$ or $< 100 \times 10^9/L$, which occurs at least 3 months after treatment, defines disease progression, if the marrow biopsy is consistent with the cytopenia resulting from increased marrow infiltration of clonal CLL cells and is not considered a treatment-related toxicity.

Stable Disease

Participants who have not achieved CR or PR, and who have not exhibited PD, will be considered to have stable disease (which is equivalent to a nonresponse).

For a detailed description of the response parameters, see [Hallek et al. 2018](#).

Appendix I Eastern Cooperative Oncology Group Performance Status Scores

Appendix Table I1 Eastern Cooperative Oncology Group Performance Status Scores

Grade	Eastern Cooperative Oncology Group performance status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Source: [Oken et al. 1982](#)

Credit: Eastern Cooperative Oncology Group Chair: Robert Comis, MD

<https://ecog-acrin.org/resources/ecog-performance-status>. Accessed 15 January 2019.

Appendix J European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30



EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:

Your birthdate (Day, Month, Year):

Today's date (Day, Month, Year):

31

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your <u>family</u> life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your <u>social</u> activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very poor

Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor

Excellent



Appendix K NCI PRO-CTCAE ITEMS

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0

English

Form created on 10 October 2018

1.	In the last 7 days, how OFTEN did you have NAUSEA?				
	☐ Never	☐ Rarely	☐ Occasionally	☐ Frequently	☐ Almost constantly
	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
2.	In the last 7 days, how OFTEN did you have VOMITING?				
	☐ Never	☐ Rarely	☐ Occasionally	☐ Frequently	☐ Almost constantly
	In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
3.	In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
4.	In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?				
	☐ Never	☐ Rarely	☐ Occasionally	☐ Frequently	☐ Almost constantly
5.	In the last 7 days, how OFTEN did you have PAIN IN THE ABDOMEN (BELLY AREA)?				
	☐ Never	☐ Rarely	☐ Occasionally	☐ Frequently	☐ Almost constantly
	In the last 7 days, what was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY AREA) at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
	In the last 7 days, how much did PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE with your usual or daily activities?				
	☐ Not at all	☐ A little bit	☐ Somewhat	☐ Quite a bit	☐ Very much

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0

English

Form created on 10 October 2018

6.	In the last 7 days, how OFTEN did you feel a POUNDING OR RACING HEARTBEAT (PALPITATIONS)?				
	☐ Never	☐ Rarely	☐ Occasionally	☐ Frequently	☐ Almost constantly
	In the last 7 days, what was the SEVERITY of your POUNDING OR RACING HEARTBEAT (PALPITATIONS)? at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe

7.	In the last 7 days, did you have any RASH?	
	☐ Yes	☐ No

8.	In the last 7 days, how OFTEN did you have a HEADACHE?				
	☐ Never	☐ Rarely	☐ Occasionally	☐ Frequently	☐ Almost constantly
	In the last 7 days, what was the SEVERITY of your HEADACHE at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
	In the last 7 days, how much did your HEADACHE INTERFERE with your usual or daily activities?				
	☐ Not at all	☐ A little bit	☐ Somewhat	☐ Quite a bit	☐ Very much

9.	In the last 7 days, how OFTEN did you have ACHING MUSCLES?				
	☐ Never	☐ Rarely	☐ Occasionally	☐ Frequently	☐ Almost constantly
	In the last 7 days, what was the SEVERITY of your ACHING MUSCLES at their WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
	In the last 7 days, how much did ACHING MUSCLES INTERFERE with your usual or daily activities?				
	☐ Not at all	☐ A little bit	☐ Somewhat	☐ Quite a bit	☐ Very much

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0

English

Form created on 10 October 2018

10.	In the last 7 days, how OFTEN did you have ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS)?				
	☐ Never	☐ Rarely	☐ Occasionally	☐ Frequently	☐ Almost constantly
	In the last 7 days, what was the SEVERITY of your ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) at their WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
	In the last 7 days, how much did ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) INTERFERE with your usual or daily activities?				
	☐ Not at all	☐ A little bit	☐ Somewhat	☐ Quite a bit	☐ Very much

11.	In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
	In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
	☐ Not at all	☐ A little bit	☐ Somewhat	☐ Quite a bit	☐ Very much

12.	In the last 7 days, did you BRUISE EASILY (BLACK AND BLUE MARKS)?	
	☐ Yes	☐ No

13.	In the last 7 days, how OFTEN did you have NOSEBLEEDS?				
	☐ Never	☐ Rarely	☐ Occasionally	☐ Frequently	☐ Almost constantly
	In the last 7 days, what was the SEVERITY of your NOSEBLEEDS at their WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe

Appendix L Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
 - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki as amended at the 64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013 and CIOMS International Ethical Guidelines
 - Applicable ICH GCP Guidelines
 - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any revised protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes is made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies and all other applicable local regulations.

Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator to AstraZeneca of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.
- AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. AstraZeneca will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/ IEC, and investigators.
- For all studies except those utilizing medical devices, investigator safety reports must be prepared for SUSAR according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review

and then file it, and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches

- Prompt notification by the investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
 - A ‘serious breach’ means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
 - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the EMA CTIS. It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The investigator should have a process in place to ensure that:
 - The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach
 - A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 4 weeks from the previous ICF signature date.
- The ICF will contain a separate section that addresses and documents the collection and use of any human biological samples. The investigator or authorized designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to withdraw their consent at any time and for any reason during the retention period.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The participant must be informed that data will be collected only for business needs. We will only collect and use the minimum amount of personal data to support our business activities and will not make personal data available to anyone (including internal staff) who is not authorized or does not have a business need to know the information.
- The participant must be informed that in some cases their data may be pseudonymized. The General Data Protection Regulation defines pseudonymization as the processing of

personal data in such a way that the personal data can no longer be attributed to a specific individual without the use of additional information, provided that such additional information is kept separately and protected by technical and organizational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.

Dissemination of Clinical Study Data

Any results, both technical and lay summaries, for this trial will be submitted to EU CTIS within a year from global End of Trial Date in all participating countries due to scientific reasons, as otherwise statistical analysis is not relevant.

A description of this clinical study will be available on <https://www.astrazenecaclinicaltrials.com> and <http://www.clinicaltrials.gov> as will the summary of the main study results when they are available. The clinical study and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted.

Data Quality Assurance

- All participant data relating to the study will be recorded on eCRFs unless transmitted to AstraZeneca or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality, such as Risk Management and Mitigation Strategies and Analytical Risk-based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are included in the Monitoring Plans or contracts.
- AstraZeneca or designee is responsible for medical oversight throughout the conduct of the study, which includes clinical reviews of study data in accordance with the currently approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the Monitoring Plans or contracts.
- AstraZeneca or designee is responsible for the data management of this study, including quality checking of the data.
- AstraZeneca assumes accountability for actions delegated to other individuals (eg, CROs).

- Study monitors will perform ongoing source data verification as per the Monitoring Plan(s) to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for a minimum of 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global retention and Disposal (GRAD) Schedule. No records may be destroyed during the retention period without the written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca.

Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or Follow-up.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix M Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

Note: For Germany, this guidance only applies to the COVID-19 pandemic. In case of further events requiring mitigation of study procedures, these will be addressed separately at the time of their occurrence.

Note: changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study participants become infected with severe acute respiratory syndrome coronavirus 2 or similar pandemic infection) during which participants may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following agreement from the AstraZeneca. For all applicable countries following EU regional guidance on the management of COVID-19 in clinical studies, refer to [EMA 2022](#) (eg, changes of monitoring, including remote source data verification and protocol deviations) and [BfArM 2022](#) for further guidance.

In cases where participants test 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.

Participants should be vaccinated if it is determined by the investigator to be in their best interest. There is no known contraindication for any of the participants on acalabrutinib studies. Participants should still protect themselves from exposure to COVID-19 after vaccination. Should the participant have AEs after immunization, the investigator is encouraged to share relevant information with the sponsor.

Dose Delays

In case of a global pandemic eg, COVID-19 infection or a natural disaster, dose delays and modifications will be allowed, and the study intervention may be held for more than 28 consecutive days due to the global pandemic infected participant treatment. Study intervention should be continued after approval of the medical monitor with a confirmed diagnosis of the cause of this dose delay or modification. Participants with COVID-19 who go off treatment for more than 28 days cannot return to the study if they progress.

Reconsent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing any procedures. Local and regional regulations and/or guidelines regarding reconsent of study participants should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the participant's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

Rescreening of Participants to Reconfirm Study Eligibility

Additional rescreening for screen failure due to study disruption can be performed in previously screened participants. The investigator should confirm this with the designated study physician.

In addition, during study disruption there may be a delay between confirming eligibility of a participant and either enrollment into the study or commencing of dosing with IP. If this delay is outside the screening window specified in Section 4.1 and Table 3, the participant will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to rescreen a participant in addition to that detailed in Section 4.1. The procedures detailed in Section 4.1 must be undertaken to confirm eligibility using the same randomization number as for the participant.

Home or Remote Visit to Replace On-site Visit

A qualified HCP from the study site or TPV service will visit the participant's home / or other remote location per local SOPs, as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the CSP.

Telemedicine Visit to Replace On-site Visit

In this appendix, and the associated Study Instruction Manual for Mitigation Due to Civil Crisis, Natural Disaster or Public Health Crisis, the term telemedicine visit refers to remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the participants will allow AEs, concomitant medication, to be reported and documented.

Data Capture During Telemedicine or Home / Remote Visits

Data collected during telemedicine or home/remote visits will be captured by the qualified HCP from the study site or TPV service, or by the participants themselves (eg, details of self-administration, PRO).

Appendix N Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment (Amendment 4) is located directly before the Table of Contents.

SUMMARY OF ADDENDUM 1 (Finland), 30 May 2023

The protocol has been amended in response to the Finnish Medicines Agency (FIMEA; the Finnish Regulatory Authority) grounds for non-acceptance dated 29 December 2022.

A summary of changes is presented in the table below.

Section number and name	Description of change with reasons
Section 3.2 Exclusion Criteria	As requested by the FIMEA, the entirety of Exclusion Criterion 4 (previously Exclusion Criterion 5 in CSPv3) is applicable to all 3 cohorts in Finland.
Section 4 Study Plan and Timing of Procedures, Table 3 Section 5.2.3 Electrocardiograms	As requested by the FIMEA, a clarification that electrolyte panel assessments must be done within 24 hours of an unscheduled ECG was added to ensure that the assessments coincide with the ECG testing.
Section 4 Study Plan and Timing of Procedures, Table 3	As requested by the FIMEA, a clarification that laboratory testing (pregnancy test, hematology, and serum chemistry) must be done in accordance with local practice after 48 cycles per physician discretion was added.
Section 4 Study Plan and Timing of Procedures, Table 3 Section 5.3.8 Hepatitis Serology and PCR	As requested by the FIMEA, a clarification that positive hepatitis B or C quantitative PCR results during screening is an Exclusion Criterion was added.
Section 4.1 Screening/Enrollment Period	As requested by the FIMEA, all tests/assessments must be performed within the screening window of 28 days. Note the exception in Table 3 Footnote “t,” which states “Molecular analysis to detect immunoglobulin heavy-chain variable (IGHV) mutation status will be done at screening only if not done at any time point before, since diagnosis.”
Section 4.3 Post-treatment Period	As requested by the FIMEA, a clarification that the SFU visit needs to be completed within 30 days and immediately before shifting to a new medication was added.
Section 5.2.5 Pregnancy Testing	As requested by the FIMEA, the time point for the additional pregnancy test when highly effective contraception is no longer required was clarified as being 2 days after the last dose of study treatment.
Appendix A Additional Safety Information	As requested by the FIMEA, text was amended to state that for tumor-related SAEs, tumors must be new tumors, and that all SAE definitions apply for all other SAEs.

Section number and name	Description of change with reasons
Appendix E Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law	As requested by the FIMEA, the terminology was changed from "liver metastases" to "liver involvement."

SUMMARY OF ADDENDUM 1 (South Korea), 01 March 2023

The protocol has been amended in response to the Ministry of Food and Drug Safety (MFDS; the South Korea Regulatory Authority) grounds for non-acceptance dated 19 December 2022.

A summary of changes is presented in the table below.

Section number and name	Description of change with reasons
Section 3.2 Exclusion Criteria	As requested by the MFDS, the entirety of Exclusion Criterion 4 is applicable to all 3 cohorts in South Korea.
Section 4.1 Screening/ Enrollment Period	As requested by the MFDS, in South Korea, hematology, serum chemistry, and creatinine clearance must be performed within 7 days of Cycle 1 Day 1 during screening, not "(6 months before screening)." All other tests/assessments must be performed within the screening window of 28 days. Note the exception in Table 3 Footnote "t," which states "Molecular analysis to detect immunoglobulin heavy-chain variable (IGHV) mutation status will be done at screening only if not done at any time point before, since diagnosis."

SUMMARY OF ADDENDUM 1 (Germany), 27 January 2023

Overall Rationale for the Addendum:

The protocol has been amended in response to the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM; the German Regulatory Authority) grounds for non-acceptance dated 05 January 2023.

A summary of changes is presented in the table below.

Section number and name	Description of change with reason
Clinical Study Protocol Synopsis	As requested by BfArM, reference to study disruptions "due to cases of civil crisis, natural disaster, or public health crisis" was replaced with "due to the COVID-19 pandemic" in these sections.
Section 3.9.1 Dose Modification	
Section 3.9.2 Temporary Discontinuation	

Section number and name	Description of change with reason
Section 4.1.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis	In response to BfArM query 1, the section heading and content was updated.
Appendix N Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis	In response to BfArM query 1, the appendix heading and content was updated.

SUMMARY OF AMENDMENT 3 (Global and UK), 20 December 2022

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment: The protocol has been amended to clarify that the addition of the important potential risk of hepatotoxicity (IBv11, 21 February 2022) classifies this amendment as Substantial. This risk was already added to CSPv3, in Section 6.1, and was considered a Substantial amendment. However, it was inadvertently not copied into the corresponding SUMMARY OF AMENDMENT 2 (22 September 2022) at the front of the protocol. This led to the initial mis-classification of CSPv3 as “Non-substantial.” Other changes in this amendment are intended to align with the latest safety data and standards for acalabrutinib, to maintain consistency, and to provide additional clarity within the protocol. Due to the COVID-19 pandemic, study mitigation language was added to be consistent with appropriate EU regional guidance, so that the clinical study can continue while minimizing risk to the participant, maintaining compliance with Good Clinical Practice, and minimizing risks to the study integrity.

List of Substantial Modifications

Section number and name	Description of change	Brief rationale
Section 6.1 Risks Associated with Acalabrutinib	Acalabrutinib IBv11 reported a new important potential risk of hepatotoxicity. This was added to CSPv3, in Section 6.1, but was inadvertently not included in the corresponding SUMMARY OF AMENDMENT 2 (22 Sep 2022; see Appendix N). This led to mis-classification of CSPv3 as “Non-substantial”	Addition of important potential risk of hepatotoxicity makes it clear that this amendment is substantial

List of Non-Substantial Modifications

Section number and name	Description of change	Brief rationale
Title page	Added EudraCT Number	In response to the Federal Institute for Drugs and Medical Devices, the German Regulatory Authority
Synopsis	Updated consistent with edits in the body of the CSP	For consistency
Section 3.2 Exclusion Criteria	Removed Exclusion Criterion 4 (regarding CNS lymphoma), which was added with Amendment 2 (CSPv3)	All participants were already recruited to this study upon submission of Amendment 2 (CSPv3). CLL-specific CNS lymphoma Exclusion Criterion remains unchanged.
Section 3.8 Drug-drug Interactions	Clarified and elaborated on existing information for caution with using St. John's wort (Appendix F) with additional verbiage about herbal remedies and dietary supplements	Clarification/elaboration
Section 3.9.1 Dose Modification Section 3.9.2.1 Temporary Discontinuation	Clarified that study treatment may be held due to civil crises, natural disasters, and public health crises	Clarification for situations similar to current civil crisis in Russia-Ukraine
Section 4 Schedule of Assessments, Footnote "r" Section 5.3.8 Hepatitis Serology and PCR	Clarified language for hepatitis serological assessment	Clarification
Section 4.1.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis Section 9.2.1 Source Data Appendix N Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis	Added EU Guidance on management of COVID-19	Modification to allow flexibility and alignment with appropriate EU regional guidance in response to the Federal Institute for Drugs and Medical Devices, the German Regulatory Authority
Section 6.10 Medication Error, Drug Abuse, and Drug Misuse Appendix A Additional Safety Information	Updated to reflect latest company protocol template guidance	Consistency with company protocol template

Section number and name	Description of change	Brief rationale
Section 9.3 Study Timetable and End of Study	Updated to reflect latest company protocol template guidance	Consistency with company protocol template
Appendix M Regulatory, Ethical, and Study Oversight Considerations	Updated to reflect latest company protocol template guidance	Consistency with company protocol template

SUMMARY OF AMENDMENT 2 (UK), 03 OCTOBER 2022

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment: The CSP (Version 2.0 for UK, dated 03 March 2020), has been amended to align with the latest safety data and standards for acalabrutinib. Due to the COVID-19 pandemic, study mitigation language was added to provide sites with measures that may be implemented, if a participant is not able to visit a study site, so that the clinical study can continue while minimizing risk to the participant, maintaining compliance with Good Clinical Practice, and minimizing risks to the study integrity. Other changes for maintaining consistency within the protocol have been made.

Section number and name	Description of change	Brief rationale
Protocol Title Page	Listed versions 2 and 3, with the respective dates.	Added new amendment version numbers and dates issued
CSP Synopsis	The information in the Synopsis was amended in line with the edits in the body of the CSP.	Updated information
	The sponsor Medical Monitor was changed.	Updated information
Section 1.1.3 Acalabrutinib	The approved indications for acalabrutinib were updated.	To align with current health authority approvals
	Summary of studies for the background information regarding acalabrutinib was updated.	To align with the latest safety data and standards
Section 1.2 Rationale for Study Design, Doses, and Control Groups	The rationale for the dosage used in the study was updated to reflect that the dosage is now regulatory-approved.	Updated information
Section 1.3 Benefit/Risk and Ethical Assessment	Assessment of the overall benefit/risk assessment was added.	To align with the latest safety data and standards

Section number and name	Description of change	Brief rationale
	The sentence “An interim safety analysis on the first 100 subjects treated for 12 cycles will occur by a Safety Monitoring Committee” was deleted from this section.	Detailed information on interim safety analysis moved to Section 1.5.
Section 1.4 Study Design	- The total number of subjects was amended from 600 to 540. - Definitions of the 3 cohorts were added. - The study design figure was updated. - Clarified that Post DCO, 2 options will be considered: patients may be transitioned to another study or may shift to a commercial supply of acalabrutinib/off-study acalabrutinib as permitted by local regulation. - Figure 1 was updated. - The duration of the study was updated.	Updated study design
Section 1.5 Study Governance and Oversight	Information regarding the interim safety analyses and the final analysis was updated.	To align with the latest safety data and standards
Section 2.1 Primary Objective	The endpoints for ECI were expanded.	To align with the statistical analysis plan (SAP)
Section 2.2 Secondary Objective	Objective response rate (ORR) was changed to overall response (OR).	OR is the endpoint at subject level, while ORR is applied to overall population.
Section 2.3 Exploratory Objectives	CCI [REDACTED]	CCI [REDACTED]
Section 3.1 Inclusion Criteria	Updated that the diagnosis of CLL that meets all published diagnostic criteria will be checked at Screening.	To meet the iwCLL 2018 criteria proposed for diagnosis of CLL subjects
	Updated Inclusion criterion #4c to specify ibrutinib and moved definition of ibrutinib intolerance from Section 1.4 Study Design to Section 3.1 Inclusion Criteria.	To provide further details

Section number and name	Description of change	Brief rationale
	Updated Inclusion criterion #7 for FISH to state it is to be conducted within 60 days during screening up to before the first dose. Results of FISH, TP53, and IGHV are not required to start subject dosing. Clarified that next-generation sequencing is preferred.	To meet the iwCLL 2018 criteria for CLL management
Section 3.2 Exclusion Criteria	New Exclusion Criterion 4 excluding history of ongoing confirmed central nervous system lymphoma.	To align with the latest safety data and standards
	Clarified that Exclusion Criterion (previously Criterion 4) applies to the prior ibrutinib therapy cohort only.	Clarification
	Added text to current Exclusion Criterion 16. “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.”	To clarify use of concomitant anticoagulant agents (direct-acting oral anticoagulants)
	Updated current Exclusion Criterion 23 to add “ongoing” interstitial lung disease.”	Clarification
Section 3.3 Subject Enrollment	Updated that the Pre-enrollment Form is required for the prior ibrutinib therapy cohort ONLY.	For sponsor to control appropriate subject recruitment
Section 3.4 Procedures for Handling Incorrectly Enrolled Subjects	Deleted text related to incorrect enrollment.	Not required per updated CSP template
	Updated with the information that no waiver for inclusion can be granted.	Clarification
Section 3.5 Methods for Assigning Treatment Groups	Updated that this is an open-label “single-arm” study	Clarification
Section 3.8 Drug-drug Interaction (New Header)	Table 1 was updated.	To align with the current safety data and standards
Section 3.9.1 Dose Modification	Dose modification instructions were updated.	To align with the current safety data and standards

Section number and name	Description of change	Brief rationale
Section 3.9.2 Discontinuation from Study Treatment	Added that subjects who discontinue treatment should complete the safety Follow-up visit within 30 days of last dose of the study treatment. Deleted statement “A subject who agrees to modified Follow-up is not considered to have withdrawn consent or to have withdrawn from the study.”	Clarification
Section 3.9.2 Discontinuation from Study Treatment	Updated the procedures for when a subject discontinues study treatment.	Clarification
Section 3.9.2.1 Temporary Discontinuation (New Section)	Added that study treatment may be held for a maximum of 28 consecutive days from expected dose due to toxicity.	To distinguish the difference between discontinuation of treatment and withdrawal from study
Section 3.10 Withdrawal from Study	Added details regarding subject withdrawal from study.	Clarification
Section 3.10.1 Screen Failures	Added information about screen failures due to COVID-19.	For mitigation due to COVID-19 pandemic
Section 3.10.2 Loss to Follow-up	Added that “a minimum of 5 contact attempts should be made.”	Clarification
Section 4 Study Plan and Timing of Procedures	- Updated treatment cycles for proper drug dispensation, and updated footnotes for clarity. - Added time window for 30-day safety Follow-up Visit. - Added that recording of adverse events and survival status will also be done post DCO. - Added that serum immunoglobulins will be checked for COVID-19 positive subjects after 2 months of cure. - Added demographics to be recorded at screening. - Added that hepatitis B virus PCR, vital signs, physical examination need to be done during post-48 cycles Follow-up. - Updated time window for EORTC-QLQ-C30 and PRO-CTCAE.	Clarification and updated information

Section number and name	Description of change	Brief rationale
	- Updated that subjects who continue in this study post-48 cycles prior to the final DCO will be followed up for safety including SAEs, AESIs, and ECIs. - Updated vital signs to include either tympanic or body temperature and the assessment of vital signs will be done after the subject has rested at least 5 minutes in the seated position. - Serum pregnancy test in females will be done at the study site. - FISH and karyotyping assessments clarified to include TP53 mutation and IGHV; and blood sampling for FISH analysis at safety Follow-up visit was removed. - Updated footnotes “x” and “y” to add that for cycles with no on-site visits, concomitant medication and AEs will be recorded via a telephone call. - Added creatinine clearance assessment to be done at all visits. - Added target/non-target lesion assessments to be performed at screening, Cycle 1 to Cycle 6, Cycle 9, Cycle 12, and then every 6 cycles. - Added urinalysis to be performed unscheduled on any visit, only if required.	
Section 4.1 Screening/Enrollment Period	A 6-month window was added such that procedures conducted as part of the subject’s routine clinical management are acceptable for screening.	Flexibility
Section 4.1.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis (New Section)	Guidance on continuing the study in the event of a serious disruption, with details of mitigation that could be employed to ensure study continuity (eg, COVID-19 pandemic).	To define a contingency plan in case of COVID-19 pandemic impact on the conduct of the study

Section number and name	Description of change	Brief rationale
Section 4.2 Treatment Period (Up to 48 Cycles)	Added clarification of cycle definition and that no dose interruptions are permitted, unless specified in the protocol. In-clinic visit frequency during treatment cycles was updated. Added the possibility of having an unscheduled visit if required, as determined by the site. Added that for cycles with no on-site visits, concomitant medications and AEs will be recorded via a telephone call. Added that WOCBP will have a Follow-up phone call to record the results of the at-home urine pregnancy test.	Clarification
Section 4.3 Post-treatment Period	- Added the time of conduct of final analysis. - Added that subjects who complete 48 cycles prior to the final DCO may be transitioned to another study or to a commercial supply of off-study acalabrutinib as permitted by local regulations.	Clarification
	A safety Follow-up (SFU) visit approximately 30 days after the last dose of study treatment was added for subjects who discontinue the study drug for any reason prior to the final DCO. Subjects who experience disease progression while on study drug, will complete the 30-day SFU visit before shifting to new medication.	Clarification
	Updated Figure 2.	To reflect changes in this protocol amendment
Section 5.1.1 Response	Allowance for an unscheduled visit for this assessment. The following information was added: Response evaluation will be done at least 1 year after initial dose of study treatment. An unscheduled visit may be conducted if required as determined by the site.	Clarification

Section number and name	Description of change	Brief rationale
Section 5.1.2 Survival	Added subjects who complete 48 cycles and continue to receive treatment post-48 cycles prior to the final DCO will be followed up until disease progression, loss to Follow-up, or death, whichever occurs first.	Clarification
Section 5.1.3.3 Administration of PRO Questionnaires	Instructions for overall PRO questionnaires completion were updated.	Updated per site manual
Section 5.2.2 Laboratory Safety Assessments	Updated information on safety assessments that may be carried out at central or local laboratories.	Clarification
	For whole blood sample analysis, added CD20, CD23, CD5, and prolymphocytes as optional analysis at screening.	Per change to the inclusion criteria
	Added creatinine clearance assessment to be done at all cycles.	Clarification and updated information
	Corrected the timing for collecting lab-related AEs.	To align with AE definition
Section 5.2.4 Vital Signs	Added either tympanic or body temperature to be recorded. Added for vital sign assessments, subject should be rested in seating position for at least 5 minutes.	Clarification
	Corrected the timing for collecting vital sign-related AEs.	To align with AE definition
Section 5.2.5 Pregnancy Testing	Added criteria for when additional pregnancy testing may be conducted.	To align with current safety standards and information
Section 5.2.6 Concomitant Medication and Subsequent Anticancer Therapies	Updated with duration of collection of concomitant medications and subsequent anticancer therapies (from screening, at every visit).	Clarification
Section 5.3.1 Medical History and Prior Medications	Added timeframe for complete medical history – from the date of CLL diagnosis.	Clarification
Section 5.3.5 Physical Examination	Corrected the timing for collecting physical exam-related AEs.	To align with AE definition
Section 5.3.9 FISH and Karyotyping	Updated criteria for FISH and karyotyping assessment.	To align with iwCLL 2018 criteria

Section number and name	Description of change	Brief rationale
Section 5.3.10 Pharmacokinetic Assessments	Updated window for pre-dose PK sample collection. Added instructions on handling of PK samples.	Clarification
Section 6.1 Risks Associated with Acalabrutinib	Entire risk section was updated.	To align with the latest safety data and standards
Section 6.1.2 Important Identified Risks (<i>New Section</i>)	Risks were organized into Important Identified or Important Potential Risks.	To align with the latest safety data and standards
Section 6.1.3 Potential Identified Risks (<i>New Section</i>)	Risks were organized into Important Identified or Important Potential Risks.	To align with the latest safety data and standards
Section 6.4 Definition of Events of Clinical Interest (<i>New Section</i>)	Added section.	To align with the latest safety data and standards
Section 6.5 Definition for Adverse Events of Special Interest	Updated AESIs.	To align with the latest safety data and standards
Section 6.6.1 Time Period for Collection of Adverse Events	Updated section; definitions were detailed.	To align with the latest safety data and standards
Section 6.6.2 Follow-up of Unresolved Adverse Events	Text was updated.	To align with the latest safety data and standards
Section 6.6.3 Variables	Seriousness criteria added as a variable for AEs and SAEs.	To align with Endpoints
Section 6.6.7 Disease Progression	Definition for progressive disease during and after therapy was added.	Clarification
Section 7.5 Compliance	Text was added to clarify subject compliance due to dose interruptions.	Clarification
Section 8.2 Sample Size Estimate	Reduced number of subjects for the prior ibrutinib therapy cohort.	Clarification
	Updated Table 7 for additional sample sizes 30, 70, and 100.	To align with analysis plans
Section 8.3 Analysis of Populations	Updated populations for statistical analysis.	To align with SAP
Section 8.5.1 Efficacy Analyses	Definitions for OR, ORR, and CCI were added.	To align with analysis plans

Section number and name	Description of change	Brief rationale
Section 8.5.2 Safety Analysis/Clinical Laboratory Tests	Modified statement to include the following: Only subjects ~~whose grades worsened~~ with a baseline and at least 1 postbaseline value will be ~~counted~~ included in the ~~numerator of percentage calculation while the denominator will be all subjects.~~	To align with SAP
Section 8.5.6 Interim Safety Analysis (New Section)	New section was added.	To align with SAP
Previous Section 8.5.6 Final Analysis	Section was deleted.	To align with analysis plans
Section 8.5.7 Data Safety Monitoring Committee (New Section)	A DSMC and its charter are described.	To align with analysis plans
Section 10.2 Subject Data Protection	Details regarding the retention period for study records were added.	Per standard requirement
Section 12 Appendices	Appendix A: Additional Safety Information - Definition of SAE clarified. - AESI list updated. - Intensity rating scale added.	To align with the latest safety data and standards
	Appendix B: (<i>New Appendix</i>) Further Guidance on the Definition of Adverse Events of Special Interest and Events of Clinical Interest Added definition and details of AESIs and ECIs.	To align with the latest safety data and standards
	Appendix D: Handling of Human Biological Samples Added information regarding chain of custody and withdrawal of informed consent for donated biological samples.	To align with the current protocol template
	Appendix E: Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law Language was updated regarding: - Potential Hy's Law cases and criteria. - Follow-up instructions were added. - Review of cases updated.	To align with the current protocol template

Section number and name	Description of change	Brief rationale
	Information regarding actions required when potential Hy's Law criteria are met before and after starting study intervention was added.	
	Appendix M: (New Appendix) Regulatory, Ethical, and Study Oversight Considerations Includes: - Regulatory and ethical considerations - Regulatory reporting requirements for SAEs - Informed consent process - Data protection - Dissemination of clinical study data - Study and site start closure - Publication policy	To align with the current protocol template.
	Appendix N: (New Appendix) Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis Adds guidance on how the study could continue in the event of a serious disruption with details of mitigation that could be employed to ensure study continuity (eg, COVID-19).	To define contingency plan in case of COVID-19 impact on the conduct of the study
	Appendix O: (New Appendix) Protocol Amendment History Added per new template and shifted all details of previous amendment here.	To align with the current protocol template

SUMMARY OF AMENDMENT 2 (GLOBAL), 22 SEPTEMBER 2022

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment: The protocol has been amended to align with the latest safety data and standards for acalabrutinib. Due to the COVID-19 pandemic, study mitigation language was added to provide sites with measures that may be implemented if a participant is not able to visit a study site, so that the clinical study can continue while minimizing risk to the participant, maintaining compliance with Good Clinical Practice, and

minimizing risks to the study integrity. Other changes for maintaining consistency within the protocol have been made.

Section number and name	Description of change	Brief rationale
Protocol Title Page	Listed amendment 2 and date issued.	Updated information.
CSP Synopsis	- The information in the Synopsis was amended in line with the edits in the body of the CSP. - The sponsor Medical Monitor was changed.	Updated information.
Section 1.1.3: Acalabrutinib	The approved indications for acalabrutinib were updated.	To align with current health authority approvals.
	Summary of studies for the background information regarding acalabrutinib was updated.	To align with the latest safety data and standards.
Section 1.2: Rationale for Study Design, Doses, and Control Groups	The rationale for the dosage used in the study was updated to reflect that the dosage is now regulatory approved.	Updated information.
Section 1.3: Benefit/Risk and Ethical Assessment	Assessment of the overall benefit/risk assessment added.	To align with the latest safety data and standards.
	The sentence “An interim safety analysis on the first 100 subjects treated for 12 cycles will occur by a Safety Monitoring Committee.” was deleted from this section.	Detailed information on interim safety analysis moved to Section 1.5.
Section 1.4: Study Design	- The total number of subjects was amended from 600 to 540. - Added definitions of the 3 cohorts. - The study design figure was updated. - Clarified that Post DCO, 2 options will be considered: patients may be transitioned to another study or may shift to a commercial supply of acalabrutinib/off-study acalabrutinib as permitted by local regulation. - Figure 1 updated. - The duration of the study was updated.	Updated study design.
Section 1.5 Study Governance and Oversight	Information regarding the interim safety analyses and the final analysis was updated.	To align with the latest safety data and standards.
Section 2.1 Primary Objective	The endpoints for ECI were expanded.	To align with the statistical analysis plan (SAP).

Section number and name	Description of change	Brief rationale
Section 2.2 Secondary Objective	Objective response rate (ORR) was changed to overall response (OR).	OR is the endpoint at subject level, while ORR is applied to overall population.
Section 2.3 Exploratory Objectives	CCI [REDACTED]	CCI [REDACTED]
Section 3.1 Inclusion Criteria	Updated that the diagnosis of CLL that meets all published diagnostic criteria will be checked at Screening.	To meet the iwCLL 2018 criteria proposed for diagnosis of CLL subjects.
	Updated inclusion criterion #4c to specify ibrutinib, and moved definition of ibrutinib intolerance from Section 1.4 Study Design to here Section 3.1 Inclusion Criteria.	To provide further details.
	Updated inclusion criterion #7 for FISH to state it is to be conducted within 60 days during screening up to before the first dose. Results of FISH, TP53, and IGHV are not required to start subject dosing. Clarified that next-generation sequencing is preferred.	To meet the iwCLL 2018 criteria for CLL management.
Section 3.2 Exclusion Criteria	New Exclusion Criterion 4 excluding history of ongoing confirmed central nervous system lymphoma.	To align with the latest safety data and standards.
	Clarified that Exclusion Criterion (previously Exclusion Criterion 4) applies to the prior ibrutinib therapy cohort only.	Clarification.
	Added text to current Exclusion Criterion 16. “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”.	To clarify use of concomitant anticoagulant agents (direct-acting oral anticoagulants).
	Updated current Exclusion Criterion 23 to add “ongoing” interstitial lung disease”.	Clarification.

Section number and name	Description of change	Brief rationale
Section 3.3 Subject Enrollment	Updated that the Pre-enrollment Form is required for the prior ibrutinib therapy cohort ONLY.	For sponsor to control appropriate subject recruitment.
Section 3.4 Procedures for Handling Incorrectly Enrolled Subjects	Deleted text related to incorrect enrollment.	Not required per updated CSP template.
	Updated with the information that no waiver for inclusion can be granted.	Clarification.
Section 3.5 Methods for Assigning Treatment Groups	Updated that this is an open-label “single-arm” study.	Clarification.
Section 3.8: Drug-drug Interaction (New Header)	Table 1 updated.	To align with the current safety data and standards.
Section 3.9.1 Dose Modification	Dose modification instructions were updated.	To align with the current safety data and standards.
Section 3.9.2 Discontinuation from Study Treatment	Added that subjects who discontinue treatment should complete the SFU visit within 30 days of last dose of the study treatment. Deleted statement “A subject who agrees to modified Follow-up is not considered to have withdrawn consent or to have withdrawn from the study”.	Clarification.
Section 3.9.2 Discontinuation from Study Treatment	Updated the procedures for when a subject discontinues study treatment.	Clarification.
Section 3.9.2.1 Temporary Discontinuation (New Section)	Added that study treatment may be held for a maximum of 28 consecutive days from expected dose due to toxicity.	To distinguish the difference between discontinuation of treatment and withdrawal from study.
Section 3.10 Withdrawal from Study	Details added regarding subject withdrawal from study.	Clarification.
Section 3.10.1 Screen Failures	Added information about screen failures due to COVID-19.	For mitigation due to COVID-19 pandemic.
Section 3.10.2 Loss to Follow-up	Added that ‘a minimum of 5 contact attempts should be made’.	Clarification.
Section 4 Study Plan and Timing of Procedures	Updated treatment cycles for proper drug dispensation, and updated footnotes for clarity.	Clarification and updated information.

Section number and name	Description of change	Brief rationale
	• Added time window for 30-day SFU Visit. • Added that recording of adverse events and survival status will also be done post DCO. • Added that serum immunoglobulins will be checked for COVID-19 positive subjects after 2 months of cure. • Added demographics to be recorded at screening. • Added that Hepatitis B Virus PCR, vital signs, physical examination need to be done during post-48 cycles Follow-up. • Updated time window for EORTC-QLQ-C30 and PRO-CTCAE. • Updated that subjects who continue in this study post-48 cycles prior to the final DCO will be followed up for safety including SAEs, AESIs, and ECIs. • Updated vital signs to include either tympanic or body temperature and the assessment of vital signs will be done after the subject has rested at least 5 minutes in the seated position. • Serum pregnancy test in females will be done at the study site. • FISH and Karyotyping assessments clarified to include TP53 mutation and IGHV; and blood sampling for FISH analysis at SFU visit was removed. • Updated footnotes 'x' and 'y' to add that for cycles with no on-site visits, concomitant medication and AEs will be recorded via a telephone call. • Added creatinine clearance assessment to be done at all visits. • Added target/non-target lesion assessments to be performed at screening, Cycle 1 to Cycle 6, Cycle 9, Cycle 12, and then every 6 cycles.	

Section number and name	Description of change	Brief rationale
	Added urinalysis to be performed unscheduled on any visit, only if required.	
Section 4.1 Screening/Enrollment Period	A 6-month window was added such that procedures conducted as part of the subject's routine clinical management are acceptable for screening.	Flexibility.
Section 4.1.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, Or Public Health Crisis (New Section)	Guidance on continuing the study in the event of a serious disruption, with details of mitigation that could be employed to ensure study continuity (eg, COVID-19 pandemic).	To define a contingency plan in case of COVID-19 pandemic impact on the conduct of the study.
Section 4.2 Treatment Period (Up to 48 Cycles)	Added clarification of cycle definition and that no dose interruptions are permitted unless specified in the protocol. In-clinic visit frequency during treatment cycles was updated. Added the possibility of having an unscheduled visit if required, as determined by the site. Added that for cycles with no on-site visits, concomitant medications and AEs will be recorded via a telephone call. Added that WOCBP will have a Follow-up phone call to record the results of the at-home urine pregnancy test.	Clarification.
Section 4.3 Post-treatment Period	- Added the time of conduct of final analysis. - Added that subjects who complete 48 cycles prior to the final DCO may be transitioned to another study or to a commercial supply of off-study acalabrutinib as permitted by local regulations.	Clarification.

Section number and name	Description of change	Brief rationale
	A safety Follow-up (SFU) visit approximately 30 days after the last dose of study treatment was added for subjects who discontinue the study drug for any reason prior to the final DCO. Subjects who experience disease progression while on study drug, will complete the 30-day SFU visit before shifting to new medication.	Clarification.
	Figure 2 updated.	To reflect changes in this protocol amendment.
Section 5.1.1 Response	Allowance for an unscheduled visit for this assessment. The following information was added: Response evaluation will be done at least 1 year after initial dose of study treatment. An unscheduled visit may be conducted if required as determined by the site.	Clarification.
Section 5.1.2 Survival	Added subjects who complete 48 cycles and continue to receive treatment post-48 cycles prior to the final DCO will be followed up until disease progression, loss to Follow-up, or death whichever occurs first.	Clarification.
Section 5.1.3.3 Administration of PRO Questionnaires	Instructions for overall PRO questionnaires completion were updated.	Updated per site manual.
Section 5.2.2 Laboratory Safety Assessments	Updated information on safety assessments that may be carried out at central or local laboratories.	Clarification.
	For whole blood sample analysis, added CD20, CD23, CD5, and prolymphocytes as optional analysis at screening.	Per change to the inclusion criteria.
	Added creatinine clearance assessment to be done at all cycles.	Clarification and updated information.
	Corrected the timing for collecting lab-related AEs.	To align with AE definition.

Section number and name	Description of change	Brief rationale
Section 5.2.4 Vital Signs	Added either tympanic or body temperature to be recorded. Added for vital sign assessments, subject should be rested in seating position for at least 5 minutes.	Clarification.
	Corrected the timing for collecting vital sign-related AEs.	To align with AE definition.
Section 5.2.5: Pregnancy Testing	Added criteria for when additional pregnancy testing may be conducted.	To align with current safety standards and information.
Section 5.2.6: Concomitant Medication and Subsequent Anticancer Therapies	Updated with duration of collection of concomitant medications and subsequent anticancer therapies (from screening, at every visit).	Clarification.
Section 5.3.1: Medical History and Prior Medications	Added timeframe for complete medical history – from the date of CLL diagnosis.	Clarification.
Section 5.3.5: Physical Examination	Corrected the timing for collecting physical exam-related AEs.	To align with AE definition.
Section 5.3.9: FISH and Karyotyping	Updated criteria for FISH and karyotyping assessment.	To align with iwCLL 2018 criteria.
Section 5.3.10: Pharmacokinetic Assessments	Updated window for pre-dose PK sample collection. Added instructions on handling of PK samples.	Clarification.
Section 6.1 Risks Associated with Acalabrutinib	Entire risk section was updated.	To align with the latest safety data and standards.
Section 6.1.2: Important Identified Risks (<i>New Section</i>)	Risks were organized into Important Identified or Important Potential Risks.	To align with the latest safety data and standards.
Section 6.1.3: Potential Identified Risks (<i>New Section</i>)	Risks were organized into Important Identified or Important Potential Risks.	To align with the latest safety data and standards.
Section 6.4 Definition of Events of Clinical Interest (<i>New Section</i>)	Section added.	To align with the latest safety data and standards.
Section 6.5 Definition for Adverse Events of Special Interest	Updated AESIs.	To align with the latest safety data and standards.

Section number and name	Description of change	Brief rationale
Section 6.6.1 Time Period for Collection of Adverse Events	Section updated, definitions detailed.	To align with the latest safety data and standards.
Section 6.6.2 Follow-up of Unresolved Adverse Events	Text updated.	To align with the latest safety data and standards.
Section 6.6.3 Variables	Seriousness criteria added as a variable for AEs and SAEs.	To align with Endpoints.
Section 6.6.7 Disease Progression	Definition for progressive disease during and after therapy was added.	Clarification.
Section 7.5 Compliance	Text was added to clarify subject compliance due to dose interruptions.	Clarification.
Section 8.2 Sample Size Estimate	Reduced number of subjects for the prior ibrutinib therapy cohort.	Clarification.
	Updated Table 7 for additional sample sizes 30, 70, and 100.	To align with analysis plans.
Section 8.3 Analysis of Populations	Updated populations for statistical analysis.	To align with SAP.
Section 8.5.1 Efficacy Analyses	Definitions for OR, ORR, and CCI were added.	To align with analysis plans.
Section 8.5.2 Safety Analysis/Clinical Laboratory Tests	Modified statement to include the following: Only subjects ~~whose grades worsened~~ with a baseline and at least one postbaseline value will be ~~counted~~ included in the ~~numerator of percentage calculation while the denominator will be~~ included in the numerator of percentage calculation while the denominator will be all subjects.	To align with SAP.
Section 8.5.6 Interim Safety Analysis (New Section)	New section was added.	To align with SAP.
Previous Section 8.5.6 Final Analysis	Section deleted.	To align with analysis plans.
Section 8.5.7 Data Safety Monitoring Committee (New Section)	A DSMC and its charter are described.	To align with analysis plans.
Section 10.2 Subject Data Protection	Details regarding the retention period for study records were added.	Per standard requirement.

Section number and name	Description of change	Brief rationale
Section 12 Appendices	Appendix A: Additional Safety Information - Definition of SAE clarified. - AESI list updated. - Intensity rating scale added.	To align with the latest safety data and standards.
	Appendix B: <i>(New Appendix)</i> Further Guidance on the Definition of Adverse Events of Special Interest and Events of Clinical Interest Added definition and details of AESIs and ECIs.	To align with the latest safety data and standards.
	Appendix D: Handling of Human Biological Samples Added information regarding chain of custody and withdrawal of informed consent for donated biological samples.	To align with the current protocol template.
	Appendix E: Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law Language was updated regarding: - Potential Hy's Law cases and criteria. - Follow-up instructions were added. - Review of cases updated. - Information regarding actions required when Potential Hy's Law criteria are met before and after starting study intervention was added.	To align with the current protocol template.
	Appendix M: <i>(New Appendix)</i> Regulatory, Ethical, and Study Oversight Considerations Includes: - Regulatory and Ethical Considerations - Regulatory Reporting Requirements for SAEs - Informed Consent Process - Data Protection - Dissemination of Clinical Study Data - Study and Site Start Closure - Publication Policy	To align with the current protocol template.

Section number and name	Description of change	Brief rationale
	Appendix N: <i>(New Appendix)</i> Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis Adds guidance on how the study could continue in the event of a serious disruption with details of mitigation that could be employed to ensure study continuity (eg, COVID-19).	To define contingency plan in case of COVID-19 impact on the conduct of the study.
	Appendix O: <i>(New Appendix)</i> Protocol Amendment History Added per new template and shifted all details of previous amendment here.	To align with the current protocol template.

SUMMARY OF AMENDMENT 1 (UK, 03 MARCH 2020)

Due to changes in study circumstances, AstraZeneca was not to enroll the treatment-naïve cohort in the study in the UK. Text was added throughout the protocol to clarify that subjects in the UK were to enroll ONLY in the relapsed/refractory cohort or the prior Bruton tyrosine kinase inhibitor cohort.

SUMMARY OF AMENDMENT 1 (GLOBAL), 13 AUGUST 2019

This amendment was considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

This protocol was amended to update the protocol according to requests made by various health authorities and to provide clarification around assessments and timing. Substantive changes (noted below) along with clarification edits and typographical corrections were made as part of this amendment.

Change	Rationale
Protocol Title Page Listed amendment 1 and date.	Added new amendment number and date issued.
CSP Synopsis Added a name and contact information for medical monitor. Updated text to be consistent with changes in the body of the protocol.	Updated sponsor information. Updated to ensure consistency.

Change	Rationale
Corrected typographic error from treatment-free survival to event-free survival.	Corrected typographic error.
Section 1.2 Rationale for Study Design, Doses and Control Groups Added sentence that Studies ACE-CL-007 and ACE-CL-309 have met their primary endpoint and achieved superiority both in TN and R/R CLL against standard of care. CCI [REDACTED]	Added updated information. CCI [REDACTED]
Section 1.4 Study Design Changed the sample size for the prior BTKi therapy cohort from "up to 70" to "approximately 70 to 100" subjects and updated number of cohorts in Figure 1. CCI [REDACTED] CCI [REDACTED] Added adverse events of special interest to the list of safety assessments.	Updated due to the growing number of subjects who have been exposed to ibrutinib as a first-line agent and the scarcity of data around retreatment with a BTKi drug. CCI [REDACTED] CCI [REDACTED] Updated text because while there have been no associated cases of ventricular arrhythmias attributed to acalabrutinib in the monotherapy clinical studies; the sponsor is aware that ibrutinib has been shown to have a risk of ventricular arrhythmia. The sponsor will collect data to ensure that there continues to be no cases of ventricular arrhythmia with acalabrutinib.
Section 1.5 Study Governance and Oversight CCI [REDACTED]	CCI [REDACTED]
Section 2.1 Primary Objective Added second primary malignancies to the list of events of clinical interest (ECIs). Added adverse events of special interest to the list of safety assessments.	Added per request from health authority. Updated text because while there have been no associated cases of ventricular arrhythmias attributed to acalabrutinib in the monotherapy clinical studies; the sponsor is aware that ibrutinib has been shown to have a risk of ventricular arrhythmia. The sponsor will continue to collect

Change	Rationale
	data to ensure that there continues to be no cases of ventricular arrhythmia with acalabrutinib.
Section 2.3 Exploratory Objectives CCI [REDACTED]	CCI [REDACTED]
Updated definition of CCI [REDACTED]	Updated for clarification.
Added an exploratory objective to characterize the pharmacokinetics of acalabrutinib and its metabolite (ACP-5862).	Added per request from health authority.
Section 3.1 Inclusion Criteria Added "(or the legal age of consent in the jurisdiction in which the study is taking place)" to criterion 1. Added "at least 1 of the following" to criterion 3. CCI [REDACTED]. Deleted statement about male condom and spermicide use in criterion 6 and added that contraception measures and restrictions on sperm donation are not required for male subjects. Clarified criterion 7 that FISH would be done within 60 days before or during screening. Added "(or legally authorized representative if allowed per local regulations)" to criterion 8.	 Added for clarification. Added for clarification. CCI [REDACTED] Added per request from health authority. Updated for clarification. Added for clarification.
Section 3.2 Exclusion Criteria CCI [REDACTED] Changed total bilirubin from > 1.5 x to > 3.0 x the upper limit of normal in criterion 17. Added Exclusion criteria #22: History of interstitial lung disease. Added 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.	CCI [REDACTED] Changed per request from health authority. Added per request from health authority. Added per request from health authority.

Change	Rationale
Section 3.3 Subject Enrollment Added "(if allowed per local regulations)" for guardian/legal representative.	Added per request from health authority.
Section 3.9.1 Dose Modification of Study Treatment Added "With and Without a Concomitant CYP3A Inducer or Inhibitor" to the title of Table 1 and in the text accompanying the table. Added to Table 1 a row labeled "Level +1" and stating that if a subject requires treatment with a strong CYP3A inducer, then the acalabrutinib dose should be increased to 200 mg bid. Clarified in the "Level-1" row to decrease acalabrutinib dose to 100 mg qd if the subject requires treatment with a moderate CYP3A inhibitor.	Added for clarity. Updated for consistency.
Section 3.9.2 Discontinuation from Study Treatment CCI [REDACTED]	CCI [REDACTED]
Section 4 Study Plan and Timing of Procedures Added an "X" in the pregnancy row of the Schedule of Assessments (SoA) to indicate that pregnancy testing will be done during Cycles 2 through 48. Added a clarification to footnote n of the SoA that for all additional testing time points, an at-home urine pregnancy test must be performed for each cycle; a Follow-up phone call will be made to the subject to confirm the results of the at-home urine pregnancy assessment. CCI [REDACTED]	Added per request from health authority. CCI [REDACTED]
Updated footnote o (hematology) and p (serum chemistry) in SoA to state that assessment will be done every cycle through Cycle 6. After Cycle 6, assessments will be done every 3 cycles through Cycle 48. Clarified in footnote v that peripheral blood will be analyzed within 60 days before or during screening for FISH and standard karyotyping. Added adverse events of special interest to the list of safety assessments in footnote y.	Added per request from health authority. Added for clarification. Updated text because while there have been no associated cases of ventricular arrhythmias attributed to acalabrutinib in the monotherapy clinical studies; the sponsor is aware that ibrutinib has been shown to have a risk of ventricular arrhythmia. The sponsor will continue to collect data to ensure that there continues to be no cases of ventricular arrhythmia with acalabrutinib.

Change	Rationale
Added to the SoA footnote ab that the time window for completing the PRO-CTCAE is ± 2 days. Added a row and corresponding footnotes ac and ad in the SoA for PK evaluation. Section 4.2 Treatment Period (Up to 48 Cycles) Clarified that starting at Cycle 13, laboratory visits will occur every 3 cycles.	Added for clarification. Added PK evaluation per request from health authority. Added per request from health authority.
Section 5.1.3.2 PRO-CTCAE Updated the CTCAE version to 5.0.	Updated for clarity.
Section 5.2.2 Laboratory Safety Assessments CCI [REDACTED]	CCI [REDACTED]
Section 5.2.5 Pregnancy Testing Added text that for all additional testing time points, an at-home urine pregnancy test must be performed for each cycle; a Follow-up phone call will be made to the subject to confirm the results of the at-home urine pregnancy assessment.	Added per request from health authority.
Section 5.3.9 FISH and Karyotyping Clarified that peripheral blood will be analyzed within 60 days before or during screening by FISH and standard karyotyping.	Added for clarification.
Section 5.3.10 Pharmacokinetic Assessments Added new section.	Added PK evaluation per request from health authority.
Section 6 Safety Reporting and Medical Management Added adverse events of special interest to the safety assessments.	Updated text because while there have been no associated cases of ventricular arrhythmias attributed to acalabrutinib in the monotherapy clinical studies; the sponsor is aware that ibrutinib has been shown to have a risk of ventricular arrhythmia. The sponsor will continue to collect data to ensure that there continues to be no cases of ventricular arrhythmia with acalabrutinib.
Section 6.1 Risks Associated with Acalabrutinib Added new section.	Add to be consistent with sponsor's other protocols.
Section 6.4 Adverse Event of Special Interest	

Change	Rationale
Added new section.	Updated text because while there have been no associated cases of ventricular arrhythmias attributed to acalabrutinib in the monotherapy clinical studies; the sponsor is aware that ibrutinib has been shown to have a risk of ventricular arrhythmia. The sponsor will continue to collect data to ensure that there continues to be no cases of ventricular arrhythmia with acalabrutinib.
Section 6.5 Recording of Adverse Events Added adverse events of special interest to the safety assessments in all required subsections of this section.	Updated text because while there have been no associated cases of ventricular arrhythmias attributed to acalabrutinib in the monotherapy clinical studies; the sponsor is aware that ibrutinib has been shown to have a risk of ventricular arrhythmia. The sponsor will continue to collect data to ensure that there continues to be no cases of ventricular arrhythmia with acalabrutinib.
Section 6.5.3 Variables Updated CTCAE version to 5.0.	Updated to newer version.
Section 6.5.5 Events of Clinical Interest Added second primary malignancies to the list of ECIs.	Added per request from health authority.
Section 6.6 Reporting of Serious Adverse Events and Adverse Events of Special Interest Added adverse events of special interest to the safety assessments and section title.	Updated text because while there have been no associated cases of ventricular arrhythmias attributed to acalabrutinib in the monotherapy clinical studies; the sponsor is aware that ibrutinib has been shown to have a risk of ventricular arrhythmia. The sponsor will continue to collect data to ensure that there continues to be no cases of ventricular arrhythmia with acalabrutinib.
Section 6.6.1 Expedited Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest Added new section.	Added per request from health authority.
Section 7.7.2 Prohibited or Restricted Concomitant Medications CCI [REDACTED] Added text that subjects requiring long-term (> 1 week) treatment with a strong CYP3A inhibitor/inducer are excluded from the study. In addition, the use of strong or moderate CYP3A inhibitors or inducers within 7 days	CCI [REDACTED] Added per request from health authority.

Change	Rationale
of the first dose of study drug is prohibited. Short-term treatment was clarified as ≤ 7 days.	
Section 8.2 Sample Size Estimate CCI Changed the sample size for the prior BTKi therapy cohort to approximately 70 to 100 subjects.	CCI Updated due to the growing number of subjects who have been exposed to ibrutinib as a first-line agent and the scarcity of data around retreatment with a BTKi drug.
Section 8.3 Definitions of Analysis Populations Clarified that subjects in the efficacy-evaluable population must have a baseline disease assessment and ≥ 1 postbaseline response assessment or have clinically assessed progression of disease. Added definition of PK-evaluable population and that PK analyses will be conducted on the PK-evaluable population.	Added for clarification. Added PK evaluation per request from health authority.
Section 8.5.2 Safety Analyses Added second primary malignancies to the list of ECIs. Added adverse events of special interest to the safety assessments. CCI	Added per request from health authority. Updated text because while there have been no associated cases of ventricular arrhythmias attributed to acalabrutinib in the monotherapy clinical studies; the sponsor is aware that ibrutinib has been shown to have a risk of ventricular arrhythmia. The sponsor will continue to collect data to ensure that there continues to be no cases of ventricular arrhythmia with acalabrutinib. CCI
Section 8.5.2.1 Adverse Events Added adverse events of special interest to the safety assessments.	Updated text because while there have been no associated cases of ventricular arrhythmias attributed to acalabrutinib in the monotherapy clinical studies; the sponsor is aware that ibrutinib has been shown to have a risk of ventricular arrhythmia. The sponsor will continue to collect data to ensure that there continues to be no cases of ventricular arrhythmia with acalabrutinib.
Section 8.5.5 Pharmacokinetic Analyses Added new section.	Added PK evaluation per request from health authority.

Change	Rationale
Section 9.2.3 Archiving of Study Documents Added text that records will be retained per local regulations.	Added per request from health authority.
Section 10.4 Informed Consent Added "or legally authorized representative (if allowed per local regulations)" to relevant bullets.	Added per request from health authority.
Section 11 References Added reference for Extermann et al. 1998 and deleted reference for Schulman et al. 2005.	Added for consistency.
Appendix A Additional Safety Information Included the definition of adverse event of special interest.	Updated text because while there have been no associated cases of ventricular arrhythmias attributed to acalabrutinib in the monotherapy clinical studies; the sponsor is aware that ibrutinib has been shown to have a risk of ventricular arrhythmia. The sponsor will continue to collect data to ensure that there continues to be no cases of ventricular arrhythmia with acalabrutinib.
Appendix D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law Updated text to be consistent with other protocols by the sponsor.	Updated for consistency.
Appendix E Known Inhibitors or Inducers of CYP3A Updated appendix to include moderate inhibitors and inducers of CYP3A.	Updated for consistency.
Appendix G Cumulative Illness Rating Scale Corrected reference to Extermann et al. 1998 .	Corrected typographic error.

SIGNATURE PAGE

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