Clinical Study Protocol	
Drug Substance	Acalabrutinib
Study Code	D8220C00007
Version	7.0
Date	7 Feb 2023

A Phase 1/2 Open Label, Multi-center Study to Assess the Safety, Tolerability, Pharmacokinetics and Clinical Efficacy of Acalabrutinib in Chinese Adult Subjects with Relapsed or Refractory Mantle Cell Lymphoma, Chronic Lymphocytic Leukemia or other B-cell Malignancies

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VERSION HISTORY

Version 7.0, 07 Feb 2023
This version update is mainly caused by Clinical Study Protocol template up-version (CSP Transcelerate - RIMS Template, TMP-0010225, Version Number 8.0). Section 4.4: Added the definition of Study Completion Date. Section 1.1 Table 3 footnote "p" and section 8.1.1.2 Follow-up: update the verbiage to “For subjects who achieve a response (CR, CRi, PR, or nPR), CT and overall response assessment must be performed for response confirmation in 12 weeks (±7 days) after the initial response imaging assessment, and then every 24 weeks (±7 days) thereafter. Hematology results must be done ±7 days of CT scans. Clinical assessments of tumor response should be done at every response assessment visit that physical exam and hematology test are performed. ” Section 8.3.5: Updated the verbiage of causality collection according to new CSP template. Updated “Investigational product” to “IMP”, added “incident” and “serious incident” situations. Section 8.4.4: Added “Drug Abuse, and Drug Misuse” in the title. Added related information and description of drug abuse and drug misuse. Section 8.5.3: Update verbiage to “Pharmacokinetic (PK) samples will be disposed of 6 months within the final Bioanalytical Report publication. ” Appendix A1: Added sub-heading “Regulatory Reporting Requirements for Serious Breaches” and related details. Appendix B8: Added the full definitions and examples of the drug abuse and drug misuse. Appendix G: Added Abbreviations of “IMP” and “NIMP”

Version 6.0, 06 Jun 2022
Section 1.1 Table 3 footnote "p" and "r", Section 8.1.1.2: correction of the typo, "PR with lymphocytosis" updated to "nPR". For subjects who achieve a response (CR, CRi, PR, or nPR), CT must be performed for response confirmation in 12 weeks (±7 days) after the initial response imaging assessment, and then every 24 weeks (±7 days) thereafter. For

subjects who achieve PR with lymphocytosis still need to perform CT every 12 weeks (±7 days) and so on through Cycle 25, and then every 24 weeks (± 7 days) thereafter.

Section 2.3.2, Section 5.1, Section 5.3, Section 6.5.2, Table 6, Section 8.2.2, Section 8.2.3, Section 8.2.5, Section 8.3.2: Updated safety information based on IB11.0 and PSSR 2.0.

Section 2.3.2.1: Added information of no contraindications are known for acalabrutinib.

Section 2.3.2.2: Updated the wording according to IB11.0 and PSSR 2.0. Update the "experience" to " important identified risks observed", added the abbreviation "HBV" and "PML" in infections part, added " Treatment- emergent" in cytopenias part, changed the " non skin carcinomas" to "non-melanoma skin carcinomas", changed "occurred" to " been reported" in Second Primary Malignancies part.

Section 2.3.2.3: Added information of Important Potential Risks.

Section 4.1.1 Added information of study conduct for risk mitigation during COVID-19 outbreak.

Section 4.4: Update wording to clarify that with exception of paper-based SAEs, no data after final DCO and electronic database closure would be collected for the purpose of this study

Section 5.1: Removed “or female partners of male subjects”. According to IB 11.0, Section 6.7.1. For male subjects with a pregnant or non-pregnant WOCBP partner, no contraception measures are required.

Section 5.3: Update the wording of restrictions of using CYP3A according to IB11.0 and PSSR 2.0. Added “Acalabrutinib is best taken with water and can be taken with or without food”. Added "Otherwise, subjects should maintain their regular diet unless modifications are required to manage an AE such as diarrhoea, nausea, or vomiting."

Section 6.5.2, Table 6: According to IB11.0 and PSSR 2.0, update the wording of co-administration of strong CYP3A inducer to clarify that acalabrutinib dose will be returned to recommended dose of 100 mg BID after stopping the strong CYP3A inducer.

Section 6.6.2: Updated the wording of dose modification according to IB11.0 and PSSR 2.0. Changed “dose de-escalation” to “dose reduction”, changed “treatment” to intervention”. Deleted “Once de-escalation was done, the dose should not restart at original dose level.” Added “Dose modification guidelines for study intervention-related toxicities are provided below. 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."

Section 6.7: Add wording "Administration of investigational product following final data cut-off will be recorded in site documents for supply management but will not be collected on the eCRF. It is recommended that investigators monitor the participant's safety laboratory results periodically during treatment with acalabrutinib in order to manage AEs, consistent with the dose modification guidelines for management of study intervention-related toxicities (see Section 6.6)."

Section 8.2: Updated the information of safety assessments, added the details of AE data and study variables (eg. vital signs, 12 lead ECG, blood sampling for haematology, clinical chemistry and coagulation, urinalysis etc.)

Section 8.2.2: Added the information of the nervous system examination, updated the wording of the lymphatic system examination, updated " physicians " to "a qualified healthcare provider". Added "Changes from baseline abnormalities should be recorded in subject notes. New or worsened clinically significant abnormalities should be recorded as AEs on the Adverse Event eCRF."

Section 8.2.3: Added "Changes from baseline abnormalities should be recorded in subject notes. New or worsened clinically significant abnormalities should be recorded as AEs on the Adverse Event eCRF."

Section 8.2.5: Added "It is recommended, where possible, that a subject's performance status be assessed by the same person throughout the study."

Section 8.3.2: Added the AEs and SAEs collection and reporting requirement. Added "All SAEs that occur during the reporting period should be followed to resolution or until the investigator assesses the subject as stable, or until the subject is lost to follow up or withdraws consent. Resolution/stable means the subject has returned to baseline state of health or the investigator does not expect any further improvement or worsening of the event."

Section 8.3.8: Updated the wording of AESI reported to clarify that AESI should be reported to sponsor within 24 hours in the eCRF.

Appendix F: Added the details on study conduct during civil crisis, natural disaster, or public health crisis, including COVID-19 outbreak.

Version 5.0, 09 Sep 2021
Section 1.1, Table 1 and Table 2: Typo error correction. Section 1.2, Section 4.1, Section 4.4: The end of trial is defined as the 3rd (instead of 2nd) analyses for R/R CLL subjects of Phase 2 cohort B. Section 1.2, Section 9.2: Revert the ORR of historical control to protocol V3 Section 2.3.2, Section 8.3.8: Updated safety information based on IB10.0 Section 4.4, Section 6.7, Section 9.5: Text is revised to be consistent with the planned analyses in the section 9. There are 2 data cut-off for rrMCL and 3 data cut-off for rr CLL. Addendum will be prepared at the 2nd data cut cut-off of each cohort A and the 3rd data cut-off of cohort B. Section 5.3: Delete the contraception restriction of male patients to keep consistency with IB. Section 8.3.2, Section 4.4, Section 6.7 and SOA annotation: Clarify the collection period of AE/SAE. Section 2.2.3.4: Updated Drug-drug interaction potential based on result of study ACE-HV-114. Section 8.4.2, Appendix B2: updated 'Congenital anomaly' wording instead of 'Congenital abnormality'. Section 8.1.1.2 (CLL tumor assessment), footnote of Table 9: Typo error correction on Footnote PR. Section 9.1: information updated as "Refer to Section 9.2 for details."

Version 4.0, 31 May 2021
Section 1.2, Section 9.2: Removed the cap for Del 17p to reflect the real distribution of del 17p in the current clinical settings. Adjusted historical control of ORR. Section 1.2, Section 9.4: Added 1st DCO for cohort B of Phase 2 portion at 6 months after LSI; 3 DCOs for cohort B of Phase 2 portion in total.

Section 1.2, Section 3, Section 9.4.4, Table 4: Added nPR category for the overall response rate throughout the protocol to keep consistency with global studies.

Section 1.2: updated study period per study reality.

Section 5.1: Updated inclusion criteria 8 per iwCLL2018 criteria and align with other CLL protocol. Target lesion criteria is different for NHL and CLL; Updated inclusion criteria 20 and removed 21 to keep consistency with IB.

Section 6.5.2 (Prohibited concomitant therapy): amended dose modification guideline for use of moderate/strong inhibitors/ inducers of CYP3A; added table to list the instructions for coadministration of drugs, to keep consistency with latest IB and SmPC. clarified that immunization with a live virus vaccine is also prohibited during study treatment.

Section 7.1.2 (Follow-up for progression and survival): to add R/R CLL content.

Section 8.1.1.1 (NHL (MCL, DLBCL, FL, SLL) tumor assessment): Added "It is recommended that disease progression identified by PET-CT alone be confirmed by an alternative imaging modality (e.g., diagnostic quality CT) or by biopsy.". A new or recurrent bone marrow involvement is one of the most frequent reasons for a PD assessment. Also to align with LY-004 protocol.

Section 8.1.1.1, footnote 'u' of Table 1 and Table 2: Clarified GI endoscopy at baseline and to keep consistent with LY-308 protocol.

Section 8.1.1.2 (CLL tumor assessment): Updated per iwCLL2018 criteria and align with other CLL protocol. Extranidal lesions are not to be selected as target lesions.

Section 8.1.1.2 (CLL tumor assessment): Corrected error in the previous version; hematology at central lab is not required for CLL subjects enrolled in Phase 1 portion.

Section 8.1.1.2 (CLL tumor assessment): Corrected error in the previous version and align with SoA Table 3 footnote.

Section 8.1.1.2 (CLL tumor assessment), footnote of Table 9: Added nPR definition per iwCLL 2018 original text.

Section 8.1.3 (Clinical laboratory assessments), footnote of Table 3: Updated the wording to clarify that no requirement to await for results for deletion 17p testing prior to enrolling (requirement is for sample to have been taken but not results been received).

Section 8.3.8 (Adverse events of special interest): Added AESI description to align with Acerta protocols at program level.

Section 8.3.11 (New cancers): Revised to be consistent with current CSP template (AZDoc0141117).

Section 8.4.2.1 (Maternal exposure): Updated the pregnancy occurs in a subject duration until 2 days after the last dose of acalabrutinib to keep consistency with IB.

Section 8.4.2.2 (Paternal exposure): Updated the wording and pregnancy occurs in a subject duration after the last dose of acalabrutinib to keep consistency with IB.

Table 1 (Schedule of Activities-Phase 1 portion): Deleted the 'X' in the 'Dispense/return of acalabrutinib' item on C1D1 and C1D8 to keep consistency with IRT design.

Table 1, 2, 3 and footnote: Clarified the "Bone marrow biopsy and aspirate" by including IHC, to consistent with the communication to site.

Table 7: Correct 1st the 2nd occurrence to be the same, to keep consistency at program level.

Appendix A, Appendix D: Updated safety language and Hy's law appendix to keep consistency at program level.

Version 3.0, 11 April 2019

The major changes in the version is to add Cohort B into Phase 2 portion to further evaluate clinical efficacy, safety and tolerability in subjects with R/R CLL subjects, Table 3 was newly added with schedule of activities of this Cohort; all sessions in protocol was also amended to reflect this major change and customized to establish consistency between initial and new cohort.

Table 1- R/R CLL subject 'B symptoms' assessment schedule; Table 1 and Table 2-HBV PCR schedule was customized to make consistency with new Phase 2 Cohort B.

Table 1 footnote c; Table 2 footnote c; Section 7.1.1 (Procedures for discontinuation of study treatment): additional scenario was added when 'end of treatment' visit is not required if other follow up visit happen nearly within short period, which is consistent with Phase 2 Cohort B.

Table 1 footnote e; Table 2 footnote d; Section 7.1.2 (Follow-up for progression and survival) was modified to indicate 'Post-treatment Disease Follow up' should continue until

disease progression, even subject receives new anticancer therapy, which is consistent with Phase 2 Cohort B.

Table 1 footnote u- was updated with note to indicate CLL subject in Phase 1 should follow different CT frequency as indicated in Table 3.

Table 1 footnote u; Table 2 footnote t- was customized with 'neck' added as required disease site in CT assessment.

The terminology of IRC (Independent Review Committee) was revised to BICR (Blinded Independent Central Review) to make consistency with AZ glossary.

New anticancer therapy evaluation was missed in original tables, it was added into Table 1, 2 and 3.

Section 1.3 (Schema): minor change on Schema to add OS Follow-up into flow.

Section 2 (Introduction): introduction of CLL disease background and role of BTK in CLL were added.

Section 3 (Objectives and Endpoints): Phase 1- efficacy endpoint for R/R CLL was clarified; Phase 2- objectives and endpoints was added for cohort B (R/R CLL).

Section 4.1 (Overall design); Section 4.4 (End of study definition); Section 6.7 (Treatment after the end of the study): the end of trial definition and subject treatment continuation after end of study is clarified in detail.

Section 5.1- inclusion criteria # 8 was modified to reflect CLL subjects must also have measurable lesion as defined; inclusion criteria # 12 was modified to remove description of bortezomib exposure; inclusion criteria #13, 15, 16 was customized to further define inclusion criteria for R/R CLL; CLL term was removed from #17 as separate criteria for R/R CLL was defined in #13~16.

Section 5.2 -exclusion criteria #4 was corrected; exclusion criteria # 22 was added to reflect subjects with prior allogeneic stem cell transplant to be excluded.

Section 5.3 (Lifestyle restrictions) was added with smoking and alcohol intake will be monitored during Phase 1 portion -intensive PK sampling period.

Section 5.4 (Screen failure): re-screen procedure was further clarified in detail.

Section 8.1.1 (Tumor assessment) was customized to allow the major change with adding R/R CLL subject tumor assessment, specific CLL tumor assessment was added into Section

8.1.1.2. NHL (MCL, DLBCL, FL, SLL) tumor assessment was also amended to be more accurate in Section 8.1.1.1.

Section 8.1.2 (Minimal Residual Disease) was newly added for R/R CLL subject in phase 2 cohort B.

Section 8.1.3 (Clinical laboratory assessments); Table 8 was added with lab assessment for R/R CLL subject efficacy and safety evaluation. 'Serum chemistry' was change to 'clinical chemistry' to allow both serum and plasma sample testing per local site practice.

Section 8.1.4 B-Symptom was defined and clarified.

Section 9.2 (Sample size determination): sample size consideration of R/R CLL patients in phase 2 cohort B was added.

Section 9.4 (Statistical analyses): Analysis plan for R/R CLL patients in phase 2 was added; Two endpoints (Time to next treatment and MRD negativity rate) for R/R CLL subjects in phase 2 were added; Censoring rule of PFS and DOR was modified.

Section 9.5 (Interim analyses) was updated to include 2 DCOs for R/R CLL subjects in phase 2.

Appendix A9 (Study and Site Closure) was updated following the latest TransCelerate template to address study termination criteria.

Version 2.0, 29 November 2018

Changes to the protocol version 1 to version 2 are summarized below.

1.2 Synopsis- National Co-ordinating Investigator's address was corrected.

1.2 Synopsis-Time Period: move out Phase 2 portion timeline with one quarter to allow time for Safety Review Committee's endorsement to initiate Phase 2 portion.

Table 1 visit window for cycle 5-12 and Table 2 visit window for Cycles 15,18, 21, ≥24 was adjusted to make consistency.

Table 1 footnote m/Table 2 footnote k/ Table 8: Blood urea nitrogen (BUN) was updated to 'urea or blood urea nitrogen' to allow more flexibility according to local lab practice.

Table 1 footnote n / Table 2 footnote o/ Table 8: HIV serology HIV-1, HIV-2 antibodies updated to HIV antibody only as more sites just provide qualitative test.

6.1.1 Manufacturer of IP was corrected to 'AstraZeneca AB'.

Table 1 footnote r/ Table 2 footnote m/ Table 8/ 8.2.2 Clinical safety laboratory assessments/ 9.4.2 Safety analyses- Monocyte cell count (CD 14) was removed as this testing does not have an impact on patient safety, and prevent patients from being followed with an unnecessary lab test.

8.5.1 Collection of pharmacokinetic samples: Exactly blood samples volumn-3mL was removed as detail information will be described in Lab Manual (as already described in protocol 8.5.1).

8.5.3 Storage and destruction of pharmacokinetic samples: Pharmacokinetic (PK) samples will be disposed of after the Bioanalytical Report finalization or six months after issuance of the draft Bioanalytical Report (whichever is earlier) unless requested for future analyses. - remove the 'unless requested for future analyses' to clearly define the PK sample destruction timeframe.

Version 1.0, 06 September 2018

Changes to the protocol are summarized below.

Table 1 and 2- abbreviations: MRD-minimal residual disease was removed to correct typo error in the initial version. Restructure table 1 and 2 to breakdown procedure. Footnote was revised to match with content change in corresponding section.

1.2 Synopsis- National Co-ordinating Investigator was added; study period is revised to reflect the latest study status.

4.1 overall design- Phase 1 portion is revised to remove RECIST 1.1 wording as it is not applicable; Phase 2 portion is revised to reflect the change of definition in the end of trial

4.1 overall design is revised to replace unacceptable drug-related toxicity with any other treatment discontinuation criterion to cover all scenarios of drug discontinuation.

4.1 overall design- study period is updated to reflect the latest status.

5.1 Inclusion criteria 10 is revised to reflect the Pathology report should be reviewed by study physician to confirm the eligibility of this criteria; inclusion criteria 13 is modified to correct typo.

6.1.1 investigational products- administration detail was added to reflect dose should be administrated approximately 12 hours apart.

6.1.2 Duration of therapy- wording was adjusted to make description more clear.

8.2.3 Physical examinations is revised to remove physician assistants, or oncology nurse practitioners preforming the lymphatic system examination to match with China clinical practice.

6.4 Treatment compliance is revised to add patient diary information.

7.1 Discontinuation of study treatment- category is re-customized to make consistence with global study.

8.1.1 Tumor assessments is updated to reflect PET/CT is not required for subject with confirmed CR, but at investigator's discretion.

8.2.2 Clinical safety lab assessments are revised to add more clarity in sample management.

8.2.3 Physician examinations is revised to reflect China medical practice.

8.2.4 Vital signs are revised to accepting of both automated device and manual device.

8.4.4 Medication Error is added.

9.4.1.3 Calculation or derivation of efficacy variables: TTR is added under 'investigator-assessed endpoints' to match with Phase 2 portion second objective endpoint.

Appendix B6 is revised to reflect oncology standard.

Appendix D3- Identification of potential Hy's Law Cases is revised to remove central laboratory wording as these testing will be done at local laboratory for this study.

Appendix E is updated to reflect new change of CYP3A inhibitors or inducers list from the FDA website.

Version 0.4, 3 May 2018
Initial creation.

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1. PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

Schedule of activities in Phase 1 portion is described in Table 1; schedule of activities in Phase 2 portion is described in Table 2 and Table 3.

Table 1 Schedule of Activities (Phase 1 portion)

	Screening [a]	Cycle 0		Cycle 1					Cycle 2		Cycle 3	Cycle 4	Cycle 5-12	Cycles 15, 18, 21 and ≥ 24[b]	EoT [c]	Safety Follow Up[d]	Post-treatment disease Follow up[e]	Survival Follow up[f]	Details in Section
		Single dose		Multiple doses															
Day of Each Cycle	**-28 to -1**	**1**	**2**	**1**	**8**	**15**	**22**	**28**	**15**	**28**	**28**	**28**	**28**	**28**					
Visit Window (Days)		**0**	**0**	**0**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**+7**	**+7**	**± 7**	**± 7**	
Informed consent	X																		Appendix A3
Hospitalization[g]	←	→	From Cycle 0 Day -1 to Cycle 0 Day 2																--
Inclusion/exclusion criteria	X																		5.1 & 5.2
Routine clinical procedures																			
Demography	X																		8
Medical history	X																		8
B symptoms	X							X[dd]		X[dd]	X[dd]	X[dd]	Cycle 5, 6, 9 and 12[dd]	Every 12W through Cycle 24, then every 24W thereafter[dd]					8.1.4

Table 1 Schedule of Activities (Phase 1 portion)

	Screening [a]	Cycle 0		Cycle 1					Cycle 2		Cycle 3	Cycle 4	Cycle 5-12	Cycles 15, 18, 21 and ≥ 24[b]	EoT [c]	Safety Follow Up[d]	Post-treatment disease Follow up[e]	Survival Follow up[f]	Details in Section
		Single dose		Multiple doses															
Day of Each Cycle	**-28 to -1**	**1**	**2**	**1**	**8**	**15**	**22**	**28**	**15**	**28**	**28**	**28**	**28**	**28**					
Visit Window (Days)		**0**	**0**	**0**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**+7**	**+7**	**± 7**	**± 7**	
Physical examination[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			8.2.2
Vital signs [i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			8.2.3
ECOG status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			8.2.5
ECG [j]	X	X			X			X		X	X	X	X	X	X	X			8.2.4
Concomitant treatments	←															→			6.5
Routine safety assessments																			
Pregnancy test[k]	X			X	As clinical indicated														8.1.3
Hematology[l]	X	X[t]		X	X	X	X	X	X	X	X	X	X	X	X	X			8.1.3
Clinical chemistry[m]	X	X[t]		X	X	X	X	X	X	X	X	X	X	X	X	X			8.1.3

Table 1 Schedule of Activities (Phase 1 portion)

	Screening [a]	Cycle 0		Cycle 1					Cycle 2		Cycle 3	Cycle 4	Cycle 5-12	Cycles 15, 18, 21 and ≥ 24[b]	EoT [c]	Safety Follow Up[d]	Post-treatment disease Follow up[e]	Survival Follow up[f]	Details in Section
		Single dose		Multiple doses															
Day of Each Cycle	**-28 to -1**	**1**	**2**	**1**	**8**	**15**	**22**	**28**	**15**	**28**	**28**	**28**	**28**	**28**					
Visit Window (Days)		**0**	**0**	**0**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**+7**	**+7**	**± 7**	**± 7**	
Hepatitis and HIV serology[n]	X																		8.1.3
HBV PCR[o]	X	Monthly from Cycle 2 through 19, every 3 months after Cycle 19 until 12 months after last dose of study drug																	8.1.3
HCV PCR[p]	X																		8.1.3
Coagulation	X	X[t]		X				X		X	X	X	X	X	X	X			8.1.3
Urinalysis[q]	X	X[t]		X				X		X	X	X	X	X	X	X			8.1.3
T/B/NK cell count [r]		X[t]		X						X			X (Cycle 6 and 12)	X (Cycle 18 and 24, then every 24 weeks)	X				8.1.3

Table 1 Schedule of Activities (Phase 1 portion)

	Screening[a]	Cycle 0		Cycle 1					Cycle 2		Cycle 3	Cycle 4	Cycle 5-12	Cycles 15, 18, 21 and ≥ 24[b]	EoT[c]	Safety Follow Up[d]	Post-treatment disease Follow up[e]	Survival Follow up[f]	Details in Section
		Single dose		Multiple doses															
Day of Each Cycle	**-28 to -1**	**1**	**2**	**1**	**8**	**15**	**22**	**28**	**15**	**28**	**28**	**28**	**28**	**28**					
Visit Window (Days)		**0**	**0**	**0**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**+7**	**+7**	**± 7**	**± 7**	
Serum Ig[s]		X[t]		X						X			X (Cycle 6 and 12)	X (Cycle 18 and 24, then every 24 weeks)	X				8.1.3
Adverse events[aa]	←															→			8.3
Efficacy measurements																			
Tumor assessments[u]																			8.1.1
CT	X									X		X	X (Cycle 6, 9 and 12)	X (every 12 weeks)			X (every 12 weeks)		8.1.1
PET-CT	X									X			Cycle 6 and to confirm CR	To confirm CR					8.1.1

Table 1 Schedule of Activities (Phase 1 portion)

	Screening [a]	Cycle 0		Cycle 1					Cycle 2		Cycle 3	Cycle 4	Cycle 5-12	Cycles 15, 18, 21 and ≥ 24[b]	EoT [c]	Safety Follow Up[d]	Post-treatment disease Follow up[e]	Survival Follow up[f]	Details in Section
		Single dose		Multiple doses															
Day of Each Cycle	**-28 to -1**	**1**	**2**	**1**	**8**	**15**	**22**	**28**	**15**	**28**	**28**	**28**	**28**	**28**					
Visit Window (Days)		**0**	**0**	**0**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**+7**	**+7**	**± 7**	**± 7**	
Bone marrow aspiration/biopsy (including IHC)[v]	X		To confirm CR															X	8.1.1
New anticancer therapy																	X	X	7.1.2
Survival Status[bb]																		X	7.1.2
Pharmacokinetic measurements																			
Pharmacokinetics		X[w]	X[w]	X[w]	X[x]			X[y]											8.5.1
Study treatment administration																			
Dispense/return of acalabrutinib		X[z]						X		X	X	X	X	X					6.1
Study drug compliance[cc]		X		X	X	X	X	X	X	X	X	X	X	X					6.4

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CR = complete remission; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EoT = End of Treatment; GI = gastrointestinal; HBV = hepatitis B virus; HCV= hepatitis C virus; HIV= human immunodeficiency virus; Ig = immunoglobulin; IHC = immunohistochemistry; Lab= laboratory; LDH = lactate dehydrogenase; LTFU = long-term follow-up; mos = months; NK cell=Natural killer cell; PCR = polymerase chain reaction; PET = positron emission tomography; PK = pharmacokinetic; PS= performance status.

Footnotes (Phase 1 portion)

a. Screening tests should be performed within 28 days before the first administration of study drug, unless otherwise indicated.
b. Treatment with acalabrutinib may be continued until disease progression or any other treatment discontinuation criterion is met. After Cycle 24, subjects will continue to have scheduled visits every 12 weeks (±3 days) as outlined on the schedule of activities.
c. End of treatment visit will be done for subjects who permanently discontinue study drug for any reason, including disease progression. (except for death, lost to follow up or withdrawal of consent). The EoT visit should be performed within 7 days of the last dose of study drugs, if possible, and is not required for subjects who discontinue from study treatment within 10 days of a scheduled study visit or if the EoT visit would be performed within 14 days of the SFU visit.
d. 30 day (+ 7 days) safety follow-up visit is required for all subjects after his or her last dose of study drug to monitor for AEs, regardless of whether the subject receives a new anticancer therapy or demonstrates disease progression within this timeframe.
e. Post-treatment Disease Follow up is only required for R/R MCL subjects, who discontinue from study treatment due to reasons other than disease progression. Subjects will be followed approximately every 12 weeks from the date of last disease evaluation until disease progression, regardless of whether the subject receives a new anticancer therapy.
f. Survival Follow up is only applicable for R/R MCL subjects who progress, but have not withdrawn consent. Subjects will be contacted approximately every 12 weeks by clinical visit or telephone until death or lost to follow up to assess survival and the use of alternative anticancer therapy.
g. Subjects should accept hospitalization at least from Cycle 0 Day -1 to Cycle 0 Day 2. Then, each subject may be discharged at an appropriate point on or after Cycle 0 Day 2 at the discretion of the investigator based on the result of assessment at discharge, which is the same as the test items performed at each pre-defined visit.
h. The physical examination includes 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 examination of palpable lymph nodes and spleen and liver below the costal margin on the respective side.
i. Vital signs (Blood pressure, pulse rate, and body temperature) should be assessed after at least 5 minutes of rest for the subject in a quiet setting without distractions (e.g., television, cell phones).
j. Twelve-lead ECGs will be obtained after the subject has been resting supine for at least 10 minutes before study-related ECGs. On the intensive PK sampling days (Cycle 0 Day 1 and Cycle 1 Day 8), the assessment will be performed at 1-2 hours post (morning) dose.
k. Women of childbearing potential only. A urine or serum pregnancy test is acceptable. Pregnancy testing can be done more frequently than the protocol-defined schedule.
l. Hematology includes complete blood count with differential and platelet counts.
m. Clinical chemistry: albumin, alkaline phosphatase, Gamma glutamyl transferase (GGT), ALT, AST, urea or blood urea nitrogen (depending on local practice), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid, triglyceride, cholesterol.
n. Hepatitis and HIV serology must include HBsAg, hepatitis B surface antibody (HBsAb), anti-HBc, hepatitis C (hepatitis C virus [HCV]) antibody and HIV antibody.
o. Subjects who are anti-HBc positive, HBsAg negative should have a quantitative PCR test for HBV DNA during screening and monthly basis from cycles 2 through 19. After Cycle 19, monitoring will occur every 3 months. HBV monitoring should continue until 12 months after last dose of study drug(s). Any subject with a rising viral load (above lower limit of detection) should discontinue study drug(s) and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B. As intravenous immunoglobulins (IVIG) may cause false positive hepatitis serology, monthly PCR testing is not required in subjects who are currently receiving or received prophylactic IVIG within 3 months 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 (e.g., in the setting of rising transaminase levels).

p. Subjects with a known history of hepatitis C or who are hepatitis C antibody positive should have quantitative PCR testing for HCV RNA performed during screening. No further testing is necessary if the PCR results are negative at screening.
q. Urinalysis: pH, ketones, specific gravity, bilirubin, protein, blood, and glucose.
r. Testing will be done by central laboratory. T/B/NK cell count (i.e., CD3, CD4, CD8, CD19, CD16/56). During Cycles ≥ 5, only done at the end of Cycles 6, 12, 18, and 24, then every 24 weeks thereafter.
s. Serum immunoglobulin: IgG, IgM, IgA. During Cycles ≥5, only done at the end of Cycles 6, 12, 18, and 24, then every 24 weeks thereafter.
t. The indicated samples at this timepoint (Cycle 0 Day 1) must be drawn predose. If screening assessments chemistry, hematology, coagulation and urinalysis are performed within 5 days prior to Cycle 0 Day 1, they do not need to be repeated at Cycle 0 Day 1.
u. **CLL subjects should follow the CT frequency in Table 3.** For subjects other than CLL, a pre-treatment CT scan with contrast (unless contraindicated) is required of the neck, chest, abdomen, and pelvis and any other disease sites within 28 days before the first dose of study drug. During treatment, CT scans with contrast (unless contraindicated) will be performed for tumor assessments at the end of Cycle 2 (± 7 days), Cycle 4 (± 7 days), and Cycle 6 (± 7 days); then every 3 cycles (12 weeks, ± 7 days) thereafter, or more frequently at the investigator's discretion. Positron-emission tomography (PET)/CT scan is only required for MCL and DLBCL subjects. A pre-treatment PET-CT scan within 60 days from first dose of study drug is required. During treatment, PET-CT scans will be performed at the end of Cycle 2 (± 7 days) and Cycle 6 (± 7 days) as well as any time to confirm CR or as clinically indicated. Subjects with confirmed CR are not required to undergo further PET-CT scans on study unless there is suspicion of progressive disease in CT but cannot be proven, PET-CT may be used at the investigator's discretion. If GI tract involvement is suspected and supported by imaging, an endoscopy at baseline should be obtained. Endoscopy is required to confirm CR for any subjects with a documented history of gastrointestinal involvement. After confirmed CR, endoscopy is not mandatory for disease evaluation.
v. Bone marrow aspiration and biopsy (including IHC) will be done at screening or within 60 days before the first dose of study drug per clinical guidelines. Bone marrow aspiration and biopsy will be performed any time to confirm CR (if bone marrow was involved by lymphoma at baseline) per clinical guidelines (see Section 8.1.1).
w. PK samples are drawn per Section 8.5.1, and timepoints are relative to the first dose; predose, 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 12, 24 and 48 hours after the first dose. The 48 hours sample should be taken before the Cycle 1 Day 1 morning dose.
x. PK samples are drawn per Section 8.5.1, and timepoints are relative to Cycle 1 Day 8 morning dose; predose, 0.25, 0.5, 0.75, 1, 2, 4, 6, 8 and 12 hours after morning dose. The 12 hours sample should be taken before the Cycle 1 Day 8 evening dose.
y. PK samples are drawn per Section 8.5.1, and timepoints are relative to Cycle 1 Day 28 morning dose; 1, 2 and 4 hours after morning dose.
z. Acalabrutinib should be taken under fasting condition (at least 10 hours before dosing and at least 4 hours after dosing) in the Phase 1 portion morning dose of Cycle 0 Day 1 and Cycle 1 Day 8.
aa. Adverse Events will be collected from time of signature of informed consent form until 30 days after the last dose of study treatment or the start of new anticancer therapy (whichever comes first). The safety follow-up period is defined as 30 (+7) days after study treatment is discontinued.
bb. Survival status should be assessed at the time of the planned final analysis and additional milestone analyses as applicable.
cc Subjects will receive a drug diary to record the specific time each dose was taken and to record reasons for any missed doses. Subject compliance will be assessed at each study visit.
dd. For R/R CLL subjects only.

Table 2 Schedule of Activities (Phase 2 Cohort A – R/R MCL)

	Screening [a]	Cycle 1					Cycle 2		Cycle 3	Cycle 4	Cycles 5-12	Cycles 15, 18, 21, ≥24 [b]	EoT [c]	Safety Follow Up [c]	Post-treatment disease Follow up [d]	Survival Follow up [e]	Details in Section
Day of Each Cycle	**-28 to -1**	**1**	**8**	**15**	**22**	**28**	**15**	**28**	**28**	**28**	**28**	**28**					
Visit Window (Days)		**0**	**± 2**				**± 2**		**± 2**	**± 2**	**± 2**	**± 3**	**+ 7**	**+ 7**	**± 7**	**± 7**	
Informed consent	x																Appendix A3
Inclusion/exclusion criteria	x																5.1 & 5.2
Routine clinical procedures																	
Demography	X																
Medical history	X																8
B symptoms	X																8.1.4
Physical examination [f]/Vital signs [g]	X	x	x	x	x	x	x	x	x	x	x	x	x	x			8.2.2 & 8.2.3
ECOG status	X	x	x	x	x	x	x	x	x	x	x	x	x	x			8.2.5
ECG [h]	X		x			x		x	x	x	x	x	x	x			8.2.4

Table 2 Schedule of Activities (Phase 2 Cohort A – R/R MCL)

	Screening [a]	Cycle 1					Cycle 2		Cycle 3	Cycle 4	Cycles 5-12	Cycles 15, 18, 21, ≥24 [b]	EoT [c]	Safety Follow Up [c]	Post-treatment disease Follow up [d]	Survival Follow up [e]	Details in Section
Day of Each Cycle	**-28 to -1**	**1**	**8**	**15**	**22**	**28**	**15**	**28**	**28**	**28**	**28**	**28**					
Visit Window (Days)		**0**	**± 2**				**± 2**		**± 2**	**± 2**	**± 2**	**± 3**	**+ 7**	**+ 7**	**± 7**	**± 7**	
Concomitant medications	←													→			6.5
Routine safety assessments																	
Pregnancy test [i]	X	x	As clinically indicated														8.1.3
Hematology [j]	X	x [r]	x	x	x	x	x	x	x	x	x	x	x	x			8.1.3
Clinical chemistry [k]	X	x [r]	x	x	x	x	x	x	x	x	x	x	x	x			8.1.3
Hepatitis and HIV serology [o]	X																8.1.3
HBV PCR [p]	X	Monthly from Cycle 2 through 19, every 3 months after Cycle 19 until 12 months after last dose of study drug															8.1.3
HCV PCR [q]	X																8.1.3
Coagulation	X	x [r]				x		x	x	x	x	x	x	x			8.1.3
Urinalysis [l]	X	x [r]				x		x	x	x	x	x	x	x			8.1.3

Table 2 Schedule of Activities (Phase 2 Cohort A – R/R MCL)

	Screening [a]	Cycle 1					Cycle 2		Cycle 3	Cycle 4	Cycles 5-12	Cycles 15, 18, 21, ≥24[b]	EoT[c]	Safety Follow Up[c]	Post-treatment disease Follow up[d]	Survival Follow up[e]	Details in Section
Day of Each Cycle	**-28 to -1**	**1**	**8**	**15**	**22**	**28**	**15**	**28**	**28**	**28**	**28**	**28**					
Visit Window (Days)		**0**	**± 2**				**± 2**		**± 2**	**± 2**	**± 2**	**± 3**	**+ 7**	**+ 7**	**± 7**	**± 7**	
T/B/NK cell count[m]		x[r]						x			Cycle 6 and 12	Cycle 18 and 24, then every 24 weeks	x				8.1.3
Serum Ig[n]		x[r]						x			Cycle 6 and 12	Cycle 18 and 24, then every 24 weeks	x				8.1.3
Adverse events[v]	←													→			8.3
Efficacy measurements																	
Tumor assessments[t]																	8.1.1
CT	x							x		x	Cycle 6, 9, and 12	x (every 12 weeks)			x (every 12 weeks)		8.1.1
PET-CT	x							x			Cycle 6 and to confirm CR	To confirm CR					8.1.1

Table 2 Schedule of Activities (Phase 2 Cohort A – R/R MCL)

	Screening [a]	Cycle 1					Cycle 2		Cycle 3	Cycle 4	Cycles 5-12	Cycles 15, 18, 21, ≥24[b]	EoT[c]	Safety Follow Up[c]	Post-treatment disease Follow up[d]	Survival Follow up[e]	Details in Section
Day of Each Cycle	**-28 to -1**	**1**	**8**	**15**	**22**	**28**	**15**	**28**	**28**	**28**	**28**	**28**					
Visit Window (Days)		**0**	**± 2**				**± 2**		**± 2**	**± 2**	**± 2**	**± 3**	**+ 7**	**+ 7**	**± 7**	**± 7**	
Bone marrow (aspirate/biopsy including IHC)[s]	x	To confirm CR															8.1.1
New anticancer therapy															x	x	7.1.2
Survival Status [w]																x	7.1.2
Pharmacokinetic measurements																	
Pharmacokinetics			X[u]	X[u]	X[u]												8.5.1
Study treatment administration																	
Dispense/return of acalabrutinib		x				x		x	x	x	x	x					6.1
Study drug compliance[x]		x	x	x	x	x	x	x	x	x	x	x					6.4

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CR = complete remission; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EoT = End of Treatment; GI = gastrointestinal; HBV = hepatitis B virus; HCV= hepatitis C virus; HIV= human immunodeficiency virus; Ig = immunoglobulin; IHC = immunohistochemistry; Lab= laboratory; LDH = lactate dehydrogenase; LTFU =

long-term follow-up; mos = months; NK cell=Natural killer cell; PCR = polymerase chain reaction; PET = positron-emission tomography; PK = pharmacokinetic; PS= performance status.

Footnotes (Phase 2- cohort A)

a. Screening tests should be performed within 28 days before the first administration of study drug, unless otherwise indicated.
b. Treatment with acalabrutinib may be continued until disease progression or any other treatment discontinuation criterion is met. After Cycle 24, subjects will continue to have scheduled visits every 12 weeks (±3 days) as outlined on the schedule of activities.
c. End of treatment visit will be done for subjects who permanently discontinue study drug early for any reason, including disease progression (except for death, lost to follow up or withdrawal of consent). The EoT visit should be performed within 7 days of the last dose of study drugs, if possible, and is not required for subjects who discontinue from study treatment within 10 days of a scheduled study visit or if the EoT visit would be performed within 14 days of the SFU visit. In addition, a 30 day (+ 7 days) safety follow-up visit is required for all subjects after his or her last dose of study drug to monitor for AEs, regardless of whether the subject receives a new anticancer therapy or demonstrates disease progression within this timeframe.
d. Post-treatment Disease Follow up visit will be done for subjects who discontinue from study treatment due to reasons other than disease progression. Subjects will be followed approximately every 12 weeks from the date of last disease evaluation until disease progression, regardless of whether the subject receives a new anticancer therapy.
e. Survival follow up visit will be done for subjects who progress but have not withdrawn consent. Subjects will be contacted approximately every 12 weeks by clinical visit or telephone until death or lost to follow up to assess survival and the use of alternative anticancer therapy
f. The physical examination includes 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 examination of palpable lymph nodes and spleen and liver below the costal margin on the respective side.
g. Vital signs (Blood pressure, pulse rate, and body temperature) should be assessed after at least 5 minutes of rest for the subject in a quiet setting without distractions (e.g., television, cell phones).
h. Twelve-lead ECGs will be obtained after the subject has been resting supine for at least 10 minutes before study-related ECGs.
i. Women of childbearing potential only. A urine or serum pregnancy test is acceptable. Pregnancy testing can be done more frequently than the protocol-defined schedule, if required by local regulatory authorities.
j. Hematology includes complete blood count with differential and platelet counts.
k. Clinical chemistry: albumin, alkaline phosphatase, Gamma glutamyl transferase (GGT), ALT, AST, urea or blood urea nitrogen (depending on local practice),calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid, triglyceride, cholesterol.
l. Urinalysis: pH, ketones, specific gravity, bilirubin, protein, blood, and glucose.
m. Testing will be done by central laboratory. T/B/NK cell count (i.e., CD3, CD4, CD8, CD19, CD16/56). During Cycles ≥5, only done at the end of Cycles 6, 12, 18, and 24, then every 24 weeks thereafter.
n. Serum immunoglobulin: IgG, IgM, IgA. During Cycles ≥5, only done at the end of Cycles 6, 12, 18, and 24, then every 24 weeks thereafter.
o. Hepatitis and HIV serology must include HBsAg, hepatitis B surface antibody (HBsAb), anti-HBc, hepatitis C (hepatitis C virus [HCV]) antibody, and HIV antibody.
p Subjects who are anti-HBc positive, HBsAg negative should have a quantitative PCR test for HBV DNA during screening and monthly basis from Cycles 2 through 19. After Cycle 19, monitoring will occur every 3 months. HBV monitoring should continue until 12 months after last dose of study drug(s). Any subject with a rising viral load (above lower limit of detection) should discontinue study drug(s) and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B. As intravenous immunoglobulins (IVIG) may cause false positive hepatitis serology, monthly PCR testing is not required in subjects who are currently receiving or received prophylactic IVIG within 3 months 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 (e.g., in the setting of rising transaminase levels).
q Subjects with a known history of hepatitis C or who are hepatitis C antibody positive should have quantitative PCR testing for HCV RNA performed during screening. No further testing is necessary if the PCR results are negative at screening.

r. The indicated samples at this timepoint (Cycle 1 Day 1) must be drawn predose. If screening assessments chemistry, hematology, coagulation and urinalysis are performed within 5 days prior to Cycle 1 Day 1, they do not need to be repeated at Cycle 1 Day 1.
s. Bone marrow aspiration and biopsy (including IHC) will be done at screening or within 60 days before the first dose of study drug per clinical guidelines. Bone marrow are required for confirmation of CR (if bone marrow was involved by lymphoma at baseline) per clinical guidelines (see Section 8.1.1).
t. A pre-treatment computed tomography (CT) scan with contrast (unless contraindicated) is required of the neck, chest, abdomen, and pelvis and any other disease sites within 28 days before the first dose of study drug. During treatment, CT scans with contrast (unless contraindicated) will be performed for tumor assessments at the end of Cycle 2 (± 7 days), Cycle 4 (± 7 days), and Cycle 6 (± 7 days); and then every 3 cycles (12 weeks, ± 7 days) thereafter, or more frequently at the investigator's discretion. A pretreatment positron-emission tomography (PET)-CT scan within 60 days from first dose of study drug is also required. During treatment, PET-CT scans will be performed at the end of Cycle 2 (± 7 days) and Cycle 6 (± 7 days) as well as any time to confirm CR or as clinically indicated. Subjects with confirmed CR are not required to undergo further PET-CT scans on study unless there is suspicion of progressive disease in CT but cannot be proven, PET-CT may be used at the investigator's discretion. If GI tract involvement is suspected and supported by imaging, an endoscopy at baseline should be obtained. Endoscopy is required to confirm CR for any subjects with a documented history of gastrointestinal involvement. After confirmed CR, endoscopy is not mandatory for disease evaluation.
u. Samples for acalabrutinib PK will be collected at 1 hour (± 0.5 hour), 2 hours (± 0.5 hour), and 4 hours (± 1 hour) after morning dose on Cycle 1 Day 8 and on Cycle 1 Day 15 or 22 (3 PK samples/visit).
v. Adverse Events will be collected from time of signature of informed consent form until 30 days after the last dose of study treatment or the start of new anticancer therapy (whichever comes first). The safety follow-up period is defined as 30 (+7) days after study treatment is discontinued.
w. Survival status should be assessed at the time of the planned final analysis and additional milestone analyses as applicable.
X. Subjects will receive a drug diary to record the specific time each dose was taken and to record reasons for any missed doses. Subject compliance will be assessed at each study visit.

Table 3 Schedule of Activities (Phase 2 Cohort B- R/R CLL)

	Screening[a]	Treatment Phase[b]									EoT Visit[c]	Safety Follow Up[c]	Post-treatment Disease Follow-up[d]	Survival Follow-up[e]	Detail in Section
Days		**Cycle 1**			**Cycle 2**		**Cycles 3 to 6**		**Cycle 7**	**Q12W starting at Cycle 10 (e.g., Cycles 10, 13, 16)-Day 1**	**At last dose**	**30 days after last dose**	**Q12W**	**Q12W**	
		1	**8**	**15**	**1**	**15**	**1**	**15**	**1**						
Visit Window (Days)	**- 28 to -1**	**0**	**± 2**		**± 2**		**± 2**			**± 2**	**+7**	**+ 7**	**± 7**	**± 7**	
Informed consent	x														Appendix A3
Inclusion/exclusion criteria	x														5.1& 5.2
Routine clinical procedures															
Demography	x														8
Medical history	x														8
Weight	x	x		x	x	x	x	x	x	x	x	x			8.2.2
Vital signs[f]	x	x	x	x	x	x	x	x	x	x	x	x			8.2.3
ECOG status	x	x			x		x		x	x	x	x			8.2.5

Table 3 Schedule of Activities (Phase 2 Cohort B- R/R CLL)

	Screening[a]	Treatment Phase[b]									EoT Visit[c]	Safety Follow Up[c]	Post-treatment Disease Follow-up[d]	Survival Follow-up[e]	Detail in Section
Days		**Cycle 1**			**Cycle 2**		**Cycles 3 to 6**		**Cycle 7**	**Q12W starting at Cycle 10 (e.g., Cycles 10, 13, 16)-Day 1**	**At last dose**	**30 days after last dose**	**Q12W**	**Q12W**	
		1	**8**	**15**	**1**	**15**	**1**	**15**	**1**						
Visit Window (Days)	**- 28 to -1**	**0**	**± 2**		**± 2**		**± 2**			**± 2**	**+7**	**+ 7**	**± 7**	**± 7**	
ECG[g]	x		x		x		x		x	x	x	x			8.2.4
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x		6.5
Safety Assessments															
Pregnancy test[h]	x	x	As clinically indicated												8.1.3
Hepatitis and HIV serology[i]	x														8.1.3
HBV PCR[j]	x	Monthly from Cycle 2 through Cycle 19, then every 3 months until 12 months after last dose of study drug													8.1.3
HCV PCR[k]	x														8.1.3
Coagulation tests	x	x[gg]			x		x		x	x	x	x			8.1.3

Table 3 Schedule of Activities (Phase 2 Cohort B- R/R CLL)

	Screening[a]	Treatment Phase[b]									EoT Visit[c]	Safety Follow Up[c]	Post-treatment Disease Follow-up[d]	Survival Follow-up[e]	Detail in Section
Days		**Cycle 1**			**Cycle 2**		**Cycles 3 to 6**		**Cycle 7**	**Q12W starting at Cycle 10 (e.g., Cycles 10, 13, 16)-Day 1**	**At last dose**	**30 days after last dose**	**Q12W**	**Q12W**	
		1	**8**	**15**	**1**	**15**	**1**	**15**	**1**						
Visit Window (Days)	**- 28 to -1**	**0**	**± 2**		**± 2**		**± 2**			**± 2**	**+7**	**+ 7**	**± 7**	**± 7**	
Clinical chemistry[l]	x	x[gg]	x	x	x	x	x		x	x	x	x			8.1.3
Urinalysis[m]	x	x[gg]			x		x		x	x	x	x			8.1.3
Serum immunoglobulins, T/B/NK counts[hh]		x[gg]					Cycle 3 only		x	Cycle 10, Cycle 13, Q24W thereafter (e.g., Cycles 19, 25)[n]			Q24W		8.1.3
Adverse events[o]	x	x	x	x	x	x	x	x	x	x	x	x			8.3
Response Evaluation [p]															
Overall response assessment[p]							Cycle 4		x	Q12W through Cycle 25, then Q24W thereafter[p]					8.1.1

Table 3 Schedule of Activities (Phase 2 Cohort B- R/R CLL)

	Screening[a]	Treatment Phase[b]									EoT Visit[c]	Safety Follow Up[c]	Post-treatment Disease Follow-up[d]	Survival Follow-up[e]	Detail in Section
Days		**Cycle 1**			**Cycle 2**		**Cycles 3 to 6**		**Cycle 7**	**Q12W starting at Cycle 10 (e.g., Cycles 10, 13, 16)-Day 1**	**At last dose**	**30 days after last dose**	**Q12W**	**Q12W**	
		1	**8**	**15**	**1**	**15**	**1**	**15**	**1**						
Visit Window (Days)	**- 28 to -1**	**0**	**± 2**		**± 2**		**± 2**			**± 2**	**+7**	**+ 7**	**± 7**	**± 7**	
Physical exam[q]	x	x			x		x		x	x	x	x	x		8.2.2
B symptoms	x				x		x		x	x			x		8.1.4
CT scans[r]	x[s]						Cycle 4		x	Q12W through Cycle 25, then Q24W thereafter [x,y]			x		8.1.1.2
Hematology[t]	x	x[gg]	x	x	x	x	x[p]		x[p]	x[p]	x	x	x		8.1.3
Bone marrow biopsy and aspirate (including IHC)[z]	x	To confirm CR[x]											As clinically indicated		8.1.1
MRD assessments	x	at PR, CR[x, aa]									x[aa]				8.1.2
Other efficacy measurements															

Table 3 Schedule of Activities (Phase 2 Cohort B- R/R CLL)

	Screening[a]	Treatment Phase[b]									EoT Visit[c]	Safety Follow Up[c]	Post-treatment Disease Follow-up[d]	Survival Follow-up[e]	Detail in Section
Days		**Cycle 1**			**Cycle 2**		**Cycles 3 to 6**		**Cycle 7**	**Q12W starting at Cycle 10 (e.g., Cycles 10, 13, 16)-Day 1**	**At last dose**	**30 days after last dose**	**Q12W**	**Q12W**	
		1	**8**	**15**	**1**	**15**	**1**	**15**	**1**						
Visit Window (Days)	**- 28 to -1**	**0**	**± 2**		**± 2**		**± 2**			**± 2**	**+7**	**+ 7**	**± 7**	**± 7**	
β2-microglobulin		x[gg]					Cycle 3 only		x	Cycle 10, Cycle 13, Q24W thereafter (e.g., Cycles 19, 25)[n]			Q24W		8.1.3
Cytogenetics and FISH panel[bb]	x										x	x			8.1.3
Genetic and molecular prognostic molecules[cc]	x										x	x			8.1.3
New anticancer therapy													x	x	7.1.2
Survival status[dd]														x	7.1.2
Pharmacokinetic measurements															
Pharmacokinetics			X[ee]	X[ee]											8.5.1

Table 3 Schedule of Activities (Phase 2 Cohort B- R/R CLL)

	Screening[a]	Treatment Phase[b]									EoT Visit[c]	Safety Follow Up[c]	Post-treatment Disease Follow-up[d]	Survival Follow-up[e]	Detail in Section
Days		**Cycle 1**			**Cycle 2**		**Cycles 3 to 6**		**Cycle 7**	**Q12W starting at Cycle 10 (e.g., Cycles 10, 13, 16)-Day 1**	**At last dose**	**30 days after last dose**	**Q12W**	**Q12W**	
		1	**8**	**15**	**1**	**15**	**1**	**15**	**1**						
Visit Window (Days)	**- 28 to -1**	**0**	**± 2**		**± 2**		**± 2**			**± 2**	**+7**	**+ 7**	**± 7**	**± 7**	
Study treatment administration															
Dispense/return of acalabrutinib		x			x		x		x	x					6.1
Study drug compliance[ff]		x	x	x	x	x	x	x	x	x					6.4

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; BID = twice daily; CR = complete remission (response); CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in situ hybridization; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV= human immunodeficiency virus; Hgb = hemoglobin level; IGHV = immunoglobulin heavy-chain variable; IHC = immunohistochemistry; INR = international normalized ratio; IVIG = intravenous immunoglobulins; MRD=minimal residual disease; NK=Natural killer; PCR = polymerase chain reaction; PET = positron-emission tomography; PK = pharmacokinetic; PLT = platelet count; PO = oral; PR= Partial response; Q12W = every 12 weeks; Q24W = every 24 weeks; QM = every month; EoT =End of Treatment.

Footnotes (Phase 2- CLL cohort)

a. Screening tests should be performed within 28 days before the first administration of study drug, unless otherwise indicated.
b. Subjects will have visits on Days 1, 8 and 15 of Cycle 1, on Days 1 and 15 of Cycles 2 to 6, on Day 1 of Cycle 7, and on Day 1 of every third cycle thereafter, starting with Cycle 10; each cycle is 28 days.

c. End of treatment (EoT) visit is required for subjects who permanently discontinue treatment early for any reason, including disease progression. (except for death, lost to follow up or withdrawal of consent). The EoT visit should be performed within 7 days of the last dose of study drugs, if possible, and is not required for subjects who discontinue from study treatment within 10 days of a scheduled study visit or if the EoT visit would be performed within 14 days of the SFU visit. A 30-day (+ 7 days) safety follow-up visit (SFU) is required for all subjects at 30 (+ 7) days after last dose of study drug to monitor for resolution or progression of AEs and to document the occurrence of any new events, regardless of whether the subject receives a new anticancer therapy or demonstrates disease progression within this timeframe.
d. Each subject should be followed until disease progression. If disease progression has not occurred at the time of the 30-day SFU visit, post-treatment disease follow-up visits should occur approximately every 3 months (12 weeks) from the date of last disease evaluation until disease progression, regardless of whether the subject receives a new anticancer therapy.
e. Once subjects progress, for all subjects who have not withdrawn consent, they will be contacted approximately every 3 months (12 weeks) by clinic visit or telephone, to assess survival and use of alternative anticancer therapy until death or lost to follow-up.
f. Vital signs (blood pressure, pulse rate, and body temperature) should be assessed after at least 5 minutes of rest for the subject in a quiet setting without distractions (e.g., television, cell phones).
g. Twelve-lead ECGs will be obtained after the subject has been resting supine for at least 10 minutes before study-related ECGs.
h. Women of childbearing potential only. A urine or serum pregnancy test is acceptable. Pregnancy testing can be done more frequently than the protocol-defined schedule.
i. Hepatitis and HIV serology must include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B core antibody (anti-HBc), hepatitis C (HCV) antibody, and HIV antibody.
j. Subjects who are anti-HBc positive, HBsAg negative should have a quantitative PCR test for HBV DNA performed during screening and every month during treatment Cycle 2 through 19. After Cycle 19, monitoring will occur every 3 months. HBV monitoring should continue until 12 months after last dose of study drug(s). Any subject with a rising viral load (above lower limit of detection) should discontinue study drug and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B. As intravenous immunoglobulins (IVIG) may cause false positive hepatitis serology, PCR testing monthly is not required in subjects who are currently receiving or received prophylactic IVIG within 3 months before study enrolment and have a documented negative anti-HBc test before the initiation of IVIG therapy. PCR testing should be performed when clinically indicated (e.g., in the setting of rising transaminase levels).
k. Subjects with a known history of hepatitis C or who are hepatitis C antibody positive should have quantitive PCR testing for HCV RNA performed during screening. No further testing beyond screening is necessary if PCR results are negative.
l. Clinical chemistry: albumin, alkaline phosphatase, Gamma glutamyl transferase (GGT), ALT, AST, urea or blood urea nitrogen (depending on local practice), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid, triglyceride, cholesterol.
m. Urinalysis: pH, ketones, specific gravity, bilirubin, protein, blood, and glucose.
n. After Cycle 7 Day 1, serum immunoglobulins, β_2-microglobulin, and T/B/NK counts should be collected every 12 weeks at Cycle 10 and Cycle 13, and every 24 weeks thereafter.
o. Adverse Events will be collected from time of signature of informed consent form until 30 days after the last dose of study treatment or the start of new anticancer therapy (whichever comes first). The safety follow-up period is defined as 30 (+7) days after study treatment is discontinued.
p. Response evaluations will be done every 12 weeks (± 7 days) with the first on-treatment radiologic assessment occurring on Cycle 4 Day 1, the second on treatment scan on Cycle 7 Day 1, and so on through Cycle 25, and then every 24 weeks (± 7 days) thereafter. For subjects who achieve a response (CR, CRi, PR, or nPR), CT and overall response assessment must be performed for response confirmation in 12 weeks (±7 days) after the initial response imaging assessment, and then every 24 weeks (±7 days) thereafter. Hematology results must be done ±7 days of CT scans. Clinical assessments should be done at every visit that physical exam and hematology test are performed.
q. The screening physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. The lymphatic system examination will include examination of palpable lymph nodes and spleen and liver below the costal margin on the respective side.

r. Radiologic imaging by CT with contrast is required and must include the neck, chest, abdomen and pelvis (and any other disease area). MRI may be used for imaging assessments if a contrast CT scan is contraindicated or unobtainable. Radiologic tumor assessment will be performed every 12 weeks (± 7 days) with the first on-treatment radiologic assessment occurring on Cycle 4 Day 1, the second on treatment scan on Cycle 7 Day 1, and so on through Cycle 25, and then every 24 weeks (± 7 days) thereafter. For subjects who achieve a response (CR, CRi, PR, or nPR), CT must be performed for response confirmation in 12 weeks (±7 days) after the initial response imaging assessment, and then every 24 weeks (±7 days) thereafter. CT scan can be performed up to 7 days before response evaluation. A central radiology vendor will be used to collect and store images for Blinded Independent Central Review (BICR).

s. Pre-treatment radiologic tumor assessment should be performed within 28 days before the first dose. Subjects who have standard of care CT results may use these results in lieu of the Screening CT required for this study, provided the CT was done within 28 days of first dose and was acquired in accordance with the guidelines outlined in Section 8.1.1.2.

t. Testing will be done by central laboratory. Hematology includes CBC with differential including, but not limited to white blood cell count, hemoglobin, hematocrit, platelet count, absolute neutrophil count (ANC), and absolute lymphocyte count (ALC).

x. Bone marrow and radiologic assessments are both required for confirmation of a CR/CRi. Bone marrow biopsies/aspirates to confirm a CR must be done between 8-12 weeks of the CT scan which showed suspected CR/CRi. Testing for minimal residual disease will be done on subjects with confirmed CRs.

y. In cases where cytopenic progression is suspected, a bone marrow aspirate or biopsy must be performed to distinguish autoimmune and drug-related cytopenias. In cases where Richter's transformation is suspected (e.g., rapidly progressive B symptoms; bulky lymphadenopathy; organomegaly; anemia; a low platelet count; and elevated serum LDH, calcium, and β2 microglobulin levels), diagnosis should be confirmed by biopsy of lymph nodes, bone marrow, or involved organs. Pathology analyses will be done for confirmation of Richter's transformation. If a whole body PET-CT scan is obtained by the Investigator as an ancillary diagnostic tool, the results of this scan should be captured in the eCRF as an unscheduled visit (these scans are not required, as biopsy of the affected site is diagnostic and sufficient for confirmation).

z. A bone marrow aspirate and biopsy (including IHC) will be done at screening or ≤ 3 months before the first dose, to confirm CR/CRi, and as clinically indicated during the post-treatment disease follow-up period.

aa. If the subject's physical examination findings, laboratory evaluations, and radiographic evaluations suggest that PR, CR or CRi has been achieved, a peripheral blood sample to evaluate MRD should be done between 8-12 weeks from the time of supportive clinical assessments including CT imaging of suspected PR, CR or CRi. A peripheral blood sample to evaluate MRD should also be done at screening and end of treatment visit or if not taken at the EoT visit, then it can be drawn at SFU visit.

bb. Peripheral blood sample will be taken at screening and at disease progression. Screening sample will be sent to a central lab testing for Del 17p, Del 13q, trisomy 12, Del 11q by FISH and stimulated karyotyping. If the progression peripheral blood sample is not taken at the EoT visit, then it can be drawn at the SFU visit.

cc. Peripheral blood sample will be taken at screening and at disease progression. Sample will be sent to central lab for testing includes, but is not limited to, sequencing of p53 mutations, immunoglobulin heavy-chain variable (IGHV) mutational status. If the progression peripheral blood sample is not taken at the EoT visit, then it can be drawn at the SFU visit.

dd. Survival status should be assessed at the time of the planned final analysis and additional milestone analyses as applicable.

ee. Samples for acalabrutinib PK will be collected at 1 hour (± 0.5 hour), 2 hours (± 0.5 hour), and 4 hours (± 1 hour) after morning dose on Cycle 1 Day 8 and on Cycle 1 Day 15 (3 PK samples/visit), if Day 15 PK collection is missed, it can be redrawn on Day 22.

ff. Subjects will receive a drug diary to record the specific time each dose was taken and to record reasons for any missed doses. Subject compliance will be assessed at each study visit.

gg. The indicated samples at this timepoint (Cycle 1 Day 1) must be drawn predose. If screening assessments chemistry, hematology, coagulation, urinalysis are performed within 5 days prior to Cycle 1 Day 1, they do not need to be repeated at Cycle 1 Day 1.

hh. T/B/NK counts will be tested by central laboratory.

1.2 Synopsis

National coordinating investigator:

PPD Beijing City, China.

Protocol Title: A Phase 1/2 Open Label, Multi-center Study to Assess the Safety, Tolerability, Pharmacokinetics and Clinical Efficacy of Acalabrutinib in Chinese Adult Subjects with Relapsed or Refractory Mantle Cell Lymphoma, Chronic Lymphocytic Leukemia or other B-cell Malignancies.

Rationale

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Overall design

This is an open-label, two-part study to assess the safety, tolerability, pharmacokinetics and clinical efficacy of acalabrutinib in Chinese adult subjects with R/R MCL, R/R CLL or other B-cell malignancies. The study is divided into 2 parts: Phase 1 portion and Phase 2 portion.

Phase 1 portion

The primary objective of Phase 1 portion is to assess the safety, tolerability and pharmacokinetics of acalabrutinib in Chinese subjects with R/R B-cell malignancies and the secondary objective is to access the efficacy of acalabrutinib in Chinese subjects with R/R B-cell malignancies. Approximately 12 subjects will be enrolled in the Phase 1 portion. The study population includes subjects with R/R non-GCB diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL).

Subjects will be administered a single dose of acalabrutinib 100 mg at Cycle 0 Day 1. During the following 2 days wash-out period, intensive PK samples will be collected before and after the first dose until pre-dose at Cycle 1 Day 1. From Cycle 1 Day 1, subjects will be administered multiple doses of acalabrutinib 100 mg BID on a continuous schedule (28 days per cycle). Intensive PK samples will be collected on Cycle 1 Day 8 for 12-hour PK profile at steady state. Additional sparse PK samples will be collected on Cycle 1 Day 28 to assess time-

dependent changes. Treatment with acalabrutinib may be continued for Cycle 2 onwards until disease progression or any other treatment discontinuation criterion is met. All subjects who discontinue the study drug will have a safety follow-up visit 30 (+7) days after the last dose of study drug.

The dose regimen of multiple doses of 100 mg BID has been found to be safe/tolerable and effective in overseas clinical studies in Western and Asian subjects. In case of intolerable toxicity, dose reduction to 100 mg QD may be considered (details in Section 6.6.2).

Phase 2 portion

Phase 2 portion is to further evaluate clinical efficacy, safety and tolerability of acalabrutinib in subjects with R/R MCL and R/R CLL. The enrolment of Phase 2 portion will be initiated per Safety Review Committee (SRC) recommendation based on preliminary safety data from Phase 1 portion. Detailed information will be provided in SRC charter. Evaluation of efficacy and safety will be performed independently for each cohort.

Cohort A

Cohort A is to evaluate clinical efficacy, safety and tolerability in subjects with pathologically documented MCL who have relapsed after or were refractory to ≥1 (but not >5) prior treatment regimens. Approximately 33 R/R MCL subjects will be enrolled to receive 100 mg of acalabrutinib BID in repeated 28-day cycles.

Cohort B

Cohort B is to evaluate clinical efficacy, safety and tolerability in subjects with CLL who have failed from ≥ 1 prior systemic therapies. Approximately 60 R/R CLL subjects will be enrolled to receive 100 mg of acalabrutinib BID in repeated 28-day cycles.

Treatment with acalabrutinib may be continued until disease progression or any other treatment discontinuation criterion is met. Dose modification provisions are outlined in Section 6.6.2. Note: Temporary withholding of study drug for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. Refer to Section 7.1 for more information on assessing disease progression under these circumstances. An early termination visit is required for any subjects who permanently discontinue study drug for any reason (except for death, lost to follow up or withdrawal of consent), including disease progression. In addition to the early termination visit, all subjects who discontinue study drug will have a safety follow-up visit 30 (+ 7) days after his or her last dose of study drug.

All subjects will have hematology, clinical chemistry, and urinalysis safety panels done at screening. Once dosing commences (Cycle 1 Day 1), all subjects will be evaluated for safety, including hematology and clinical chemistry at regular basis.

Tumor assessments for R/R MCL subjects will be performed at 8- to 12-week intervals throughout the study. Tumor assessments for R/R CLL subjects will be performed at 12- to 24-week intervals throughout the study.

Refer to Section 1.1 for a comprehensive list of study assessments and their timing. The end of trial is defined as the 3rd analyses for R/R CLL subjects of Phase 2 cohort B, which will occur approximately 24 months after the last R/R CLL subject enrolled into Phase 2.

The primary efficacy analysis (R/R MCL and R/R CLL subjects) will be based on Independent Review Committee assessment.

Objectives and Endpoints	
Phase 1 Portion - Primary Objective:	**Endpoint/Variable:**
To assess the safety and tolerability of acalabrutinib in Chinese subjects with R/R B-cell malignancies	AEs, laboratory data, vital signs, and ECGs
To characterize pharmacokinetics of acalabrutinib and its major metabolite (ACP-5862) in Chinese subjects with R/R B-cell malignancies	AUCinf, AUC0-12, AUClast, Cmax, tmax, CL/F (acalabrutininb only), Vz/F (acalabrutininb only), λz, t½λz, Metabolite: Parent ratio (Cmax), and Metabolite: Parent ratio (AUC) after single dose; AUCτ , Cmax, Cmin, tmax, CL/F (acalabrutinib only), Metabolite: Parent ratio (Cmax), Metabolite: Parent ratio (AUCτ), TCP, Rac AUC and Rac Cmax after multiple doses
Phase 1 Portion - Secondary Objective:	**Endpoint/Variable:**
To assess the efficacy of acalabrutinib in Chinese subjects with R/R B-cell malignancies	For R/R CLL: Tumor response (number of patients with CR, CRi, PR, nPR, PRL, SD, PD) For other R/R B-cell malignancies: Tumor response (number of patients with CR, PR, SD, PD)
Phase 2 Portion Cohort A - Primary Objective:	**Endpoint/Variable:**
To assess the efficacy of acalabrutinib in Chinese subjects with R/R MCL	ORR as assessed by BICR per Lugano classification for NHL (Cheson 2014)
Phase 2 Portion Cohort A- Secondary Objective:	**Endpoint/Variable:**
To further assess the efficacy of acalabrutinib in Chinese subjects with R/R MCL	DoR, PFS and TTR as assessed by BICR per Lugano classification for NHL (Cheson 2014); ORR, DoR, PFS and TTR as assessed by investigators per Lugano classification for NHL (Cheson 2014); OS
To assess the safety profile of acalabrutinib in Chinese subjects with R/R MCL	AEs, laboratory parameters, vital signs, and ECGs
To assess pharmacokinetics of acalabrutinib in Chinese subjects with R/R MCL	Plasma concentration of acalabrutinib (sparse sampling)

Objectives and Endpoints	
Phase 2 Portion Cohort B- Primary Objective:	**Endpoint/Variable:**
To assess the efficacy of acalabrutinib in Chinese subjects with R/R CLL	ORR as assessed by BICR per iwCLL 2018 criteria
Phase 2 Portion Cohort B- Secondary Objective:	**Endpoint/Variable:**
To further assess the efficacy of acalabrutinib in Chinese subjects with R/R CLL	DoR, PFS and TTR as assessed by BICR per iwCLL 2018 criteria; ORR, DoR, PFS and TTR as assessed by investigators per iwCLL 2018 criteria; TTNT; CCI [redacted]
To assess the safety profile of acalabrutinib in Chinese subjects with R/R CLL	AEs, laboratory parameters, vital signs, and ECGs
To assess pharmacokinetics of acalabrutinib in Chinese subjects with R/R CLL	Plasma concentration of acalabrutinib (sparse sampling)
Safety Objectives are contained within the primary and secondary objectives.	

Data from R/R MCL subjects in both Phase 1 and Phase 2 will be combined for analysis.

Study Period

Study period		Phase of development
Estimated date of first subject enrolled	Q2, 2020	Phase 1 portion
Estimated date of last subject completed Phase 1 portion	Q2, 2022	Phase 1 portion
Estimated date of first subject enrolled Phase 2 portion	Q3, 2020	Phase 2 portion
Estimated date of last subject completed Phase 2 portion	Q4, 2023	Phase 2 portion

Number of Subjects

Approximately 12 Chinese subjects with R/R B-cell malignancies will be enrolled in Phase 1 portion. Approximately 33 Chinese subjects with R/R MCL (cohort A) and 60 Chinese subjects with R/R CLL (cohort B) will be enrolled in Phase 2 portion.

Treatments and treatment duration

In Phase 1 portion, all eligible subjects will first receive a single dose of acalabrutinib 100 mg and after 2 days washout period, the subjects will start to be treated at a continuous dosing of

acalabrutinib twice daily until disease progression or any other treatment discontinuation criteria is met.

In Phase 2 portion, all eligible subjects will be treated at a continuous dosing of acalabrutinib 100 mg BID until disease progression or any other treatment discontinuation criterion is met.

Statistical methods

Approximately 12 subjects will be enrolled in Phase 1 portion. Additional subjects may be enrolled to ensure at least 8 eligible subjects with evaluable single- and multiple-dose PK profiles based on China regulatory recommendations. Approximately 93 subjects will be enrolled in Phase 2 portion (33 subjects with R/R MCL in cohort A and 60 subjects with R/R CLL in cohort B). A sample size of 33 subjects with R/R MCL (cohort A) will provide a 95% two-sided confidence interval centred around an expected ORR of 80% that excludes an ORR of 60% as a lower bound. With 60 subjects from R/R CLL (cohort B), an exact binomial test with a nominal one-sided 2.5% significance level will have 90% power to detect the difference between a null hypothesis ORR of 70% and an alternative ORR of 88%.

All subjects who receive at least one dose of acalabrutinib will be included in safety analysis set and used for safety reporting. Safety data will not be formally analyzed. The number and percent of subjects with treatment-emergent adverse events (TEAEs) will be summarized. Summary of other safety parameters will be provided where appropriate. The safety summaries will be produced for Phase 1 and Phase 2 portion, separately. As for Phase 2 portion, safety parameters will be summarized by each cohort.

All subjects who received at least one dose of acalabrutinib and for whom baseline tumor assessment is available will be included in tumor response set and used for efficacy analyses. Regarding anti-tumor assessment, data from R/R MCL subjects in both Phase 1 and Phase 2 will be combined for analysis. Whereas, efficacy analysis of tumor response in R/R CLL will

only be applied for R/R CLL subjects in Phase 2. ORR with corresponding 95% exact CIs will be presented by each cohort.

There are two planned analyses for all subjects of Phase 1 portion and cohort A of Phase 2 portion.

The data cut-off for 1st analysis will take place when both of the following two conditions are met

- Approximately 1 month after Cycle 1 day 1 of the last subject in Phase 1 to allow required PK samplings at cycle 0 and cycle 1 are collected.
- Approximately 6 months after last R/R MCL subjects in across both Phase 1 and Phase 2 to allow a minimum of two tumor assessments after first dose.

A Clinical Study Report will be prepared to summarize PK, safety and efficacy data for Phase 1 portion and/or cohort A of Phase 2 portion. R/R MCL subjects in Phase 1, if applicable, will be combined together with the subjects in cohort A of Phase 2 portion for MCL analysis.

The data cut-off for 2nd analysis will take place approximately 14 months after last subject enrolled in both Phase 1 and cohort A of Phase 2. A Clinical Study Report Addendum including all subjects of Phase 1 portion and/or cohort A of Phase 2 portion will be prepared at that time.

There are three planned analyses for R/R CLL subjects of cohort B of Phase 2 portion.

The data cut-off for 1st analysis will take place when approximately 6 months after last R/R CLL subjects enrolled in Phase 2. A Clinical Study Report will be prepared to summarize efficacy, safety and PK data for cohort B of Phase 2 portion. Efficacy analysis of tumor response in R/R CLL will only be applied for R/R CLL subjects in Phase 2. Tumor response of R/R CLL subjects in Phase 1 may be listed separately in a proper way.

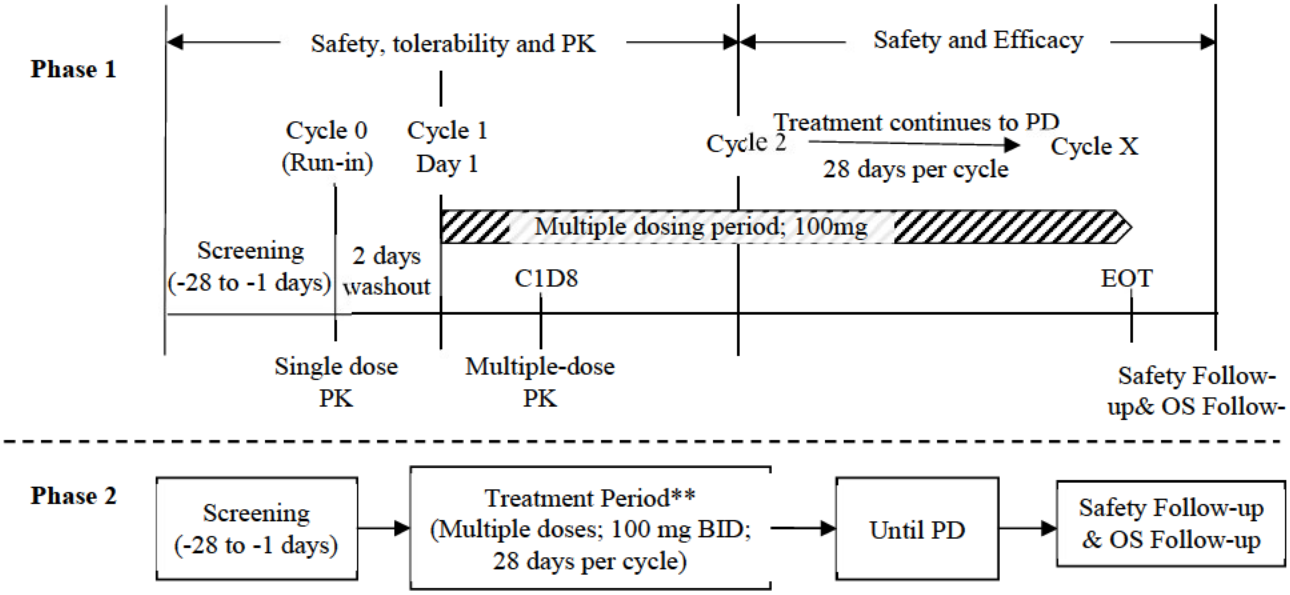
The data cut-off for 2nd analysis will take place when approximately 12 months after last R/R CLL subject enrolled in Phase 2. A Clinical Study Report Addendum including R/R CLL subjects of cohort B of Phase 2 portion will be prepared at that time.

The data cut-off for 3rd analysis will take place approximately 24 months after last R/R CLL subject enrolled in Phase 2. A Clinical Study Report Addendum including R/R CLL subjects of cohort B of Phase 2 portion will be prepared at that time.

1.3 Schema

The general study design is summarized in Figure 1.

Figure 1 Study design



* Dose reduction to 100 mg QD may be considered

** Sparse PK sampling will be collected

2. INTRODUCTION

2.1 Study rationale

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[redacted]

2.2 Background

2.2.1 Disease Background

Non-Hodgkin's lymphomas (NHL) are a heterogeneous group of lymphoproliferative disorders originating in B-lymphocytes, T-lymphocytes or natural killer (NK) cells. NHL is the seventh leading disease of new cancer cases among men and women, accounting for 4% of new cancer cases and 3% of cancer-related deaths in US.

MCL is a distinct subtype of NHL comprising approximately 7% of all adult NHL in US, with a moderately aggressive clinical course and poor outcome. The primary cell of origin of MCL is thought to be a naive B cell of pre-germinal center origin within the mantle zone of the lymph node. The incidence of MCL increases with age and an increase in incidence has been observed over time (Zhou 2008). Translocation t (11;14) (q13;q32) and overexpression of cyclin D1 are the defining characteristics in the vast majority of cases of MCL, facilitating malignant transformation by dysregulation of the cell cycle.

Although high response rates have been reported in the front-line setting with combination chemotherapy and stem-cell transplant, most of these patients eventually relapse and die from their disease (Romaguera 2010). Median overall survival (OS) from initial diagnosis varies from 18 to 61 months depending on prognostic risk category at baseline (Hoster 2008). Median progression-free survival (PFS) for relapsed MCL varies from 4 to 14 months (Wang 2013; Goy 2013). Effective therapy for relapsed MCL is therefore an unmet medical need.

In China, an estimated 882000 people were diagnosed with lymphoma and there were approximately 521000 deaths due to the disease in 2015 (Chen 2015). MCL represents about 3% of all the NHLs in China (Li 2011). Disease biology and treatment paradigm are generally aligned between China and US (Ma 2016). Treatment of patients with R/R MCL remains a major challenge as well.

CLL is the most common adult leukemia in US with an estimated incidence of 3.3–6.4 cases per 100,000/year (Eichhorst 2015). The incidence rate in Asia, including China, is lower at <1 case per 100,000/year (Redaelli 2004; Yang 2015). The treatment of CLL has progressed

significantly over the previous decades. However, CLL remains an incurable disease with relapse inevitable and most patients requiring multiple lines of therapy. Therapeutic choice after relapse requires the evaluation of the intensity of the previous therapies, the duration of response to those therapies, and patient comorbidities. In the last decade targeted therapies against B cell markers/antigens or against components of the B cell receptor such as BTK or PI3K have demonstrated efficacy with less toxicity (Wiestner 2015). However, newer therapies with less toxicity and stronger and more durable responses are still needed for the treatment of R/R CLL, especially in China.

2.2.2 Role of BTK in Lymphoid Cancers

Bruton tyrosine kinase (BTK) is a non-receptor enzyme of the Tec kinase family that is expressed among cells of hematopoietic origin, including B cells, myeloid cells, mast cells and platelets, where it regulates multiple cellular processes including proliferation, differentiation, apoptosis, and cell migration (Mohamed 2009, Bradshaw 2010). Functional null mutations of BTK in humans cause the inherited disease, X-linked agammaglobulinemia, which is characterized by a lack of mature peripheral B cells (Vihinen 2000). Conversely, BTK activation is implicated in the pathogenesis of several B-cell malignancies (Buggy 2012). Taken together, these findings have suggested that inhibition of BTK may offer an attractive strategy for treating B-cell neoplasms.

Ibrutinib (IMBRUVICA®), a first-generation oral, small-molecule BTK inhibitor has been approved for the treatment for chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL). The pivotal study of ibrutinib for the treatment of MCL showed that 75 of the 111 treated subjects (68%) had a reduction of ≥ 50% in lymphadenopathy (Wang 2013). The most frequently reported AEs in the study were diarrhea (50%, Grade 3: 6%), fatigue (41%, Grade 3: 5%), and nausea (31%, no Grade 3 AEs). Grade 3 and 4 hematologic AEs included neutropenia (in 16% of patients), thrombocytopenia (in 11%), and anemia (in 10%). Grade 3 bleeding AEs were reported in 5 patients, and 4 patients had subdural hematomas. The pivotal study of ibrutinib for the treatment of CLL showed that overall response rate was significantly higher in the ibrutinib group than in the ofatumumab group (42.6% vs. 4.1%, P<0.001) (Byrd 2014). The most frequent nonhematologic AE were diarrhea (48%, Grade 3 or 4: 4%), fatigue (28%, Grade 3 or 4: 2%), pyrexia (24%, Grade 3 or 4: 2%), and nausea (26%, Grade 3 or 4: 2%) in the ibrutinib group. Grade 3 and 4 hematologic AEs included neutropenia (in 16% of patients), thrombocytopenia (in 6%), and anemia (in 5%). Major hemorrhage (any hemorrhagic event of grade 3 or higher or resulting in transfusion of red cells or in hospitalization) was reported in 2 patients (1%) in the ibrutinib group (including 1 patient with a subdural hematoma).

While highly potent in inhibiting BTK, ibrutinib has also shown in vitro activity against other kinases with a cysteine in the same position as Cys481 in BTK to which the drug covalently binds. The inhibition of epidermal growth factor receptor (EGFR) is also observed in cellular

assays and may be the cause of ibrutinib-related adverse events (AEs) of diarrhea and rash (IMBRUVICA® package insert). In addition, ibrutinib is a substrate for CYP3A; inhibition of CYP3A causes a 29-fold increase in maximum concentration (Cmax), and 24-fold increase in area under the curve (AUC) for ibrutinib (IMBRUVICA® package insert). This increases the possibility of drug-drug interactions in combination therapies with drugs currently used in management of subjects with cancer. These liabilities support the development of alternative BTK inhibitors for use in the therapy of B-cell malignancies.

In particular, ibrutinib was approved in China for treatment of adult patients with MCL or CLL/SLL who have received at least one prior therapy. And it was approved for previously untreated CLL/SLL in China in 2018. However, clinical data of ibrutinib in this Chinese population is still very limited.

2.2.3 Acalabrutinib

Acalabrutinib is an imidazopyrazine analogue with a molecular weight of 465.5 g/mol. The compound has 1 chiral center and acalabrutinib is the S-enantiomer. Acalabrutinib is orally administered and is suitable for formulating in capsules. For clinical testing, acalabrutinib has been manufactured and formulated according to current Good Manufacturing Practices (cGMP).

2.2.3.1 Mechanism of Action

Acalabrutinib was specifically designed to be a more selective inhibitor of BTK to avoid off-target side effects seen with other BTK inhibitors (Byrd 2016). When profiled against 395 human kinases (including epidermal growth factor receptor [EGFR], TEC, JAK), acalabrutinib is more selective than ibrutinib (Covey 2015). For additional details, refer to the Acalabrutinib Investigator Brochure.

2.2.3.2 Safety Pharmacology

In vitro and in vivo safety pharmacology studies with acalabrutinib have demonstrated a favorable nonclinical safety profile; for detailed information on the safety pharmacology of acalabrutinib, refer to the Investigator Brochure.

2.2.3.3 Clinical Pharmacology

Acalabrutinib has a short PK half-life with a long-lasting pharmacodynamic effect due to covalent binding to BTK.

Acalabrutinib is highly permeable, and is rapidly and nearly completely absorbed after oral dosing over the studied dose range up to 400 mg. Acalabrutinib solubility is pH-dependent across the physiologic pH range; however, solubility is high in acidic conditions up to pH 4 (e.g., normal gastric pH). PK properties of acalabrutinib in healthy adult subjects were evaluated after oral administration of 2 daily divided doses of 2.5 to 50 mg and a single dose

of 100 mg. Acalabrutinib plasma tmax values were between 0.5 and 1.0 hour for all dose cohorts, and were independent of dose level. Mean half-life values ranged from 0.97 hours to 2.1 hours.

Acalabrutinib has an absolute oral bioavailability of 25% (range 20% to 30%) and can be taken with or without food. Acalabrutinib does not accumulate in plasma upon repeat-dose administration. Based on population PK analysis, acalabrutinib PK was linear over the 75 to 250 mg dose range. At a dose of 100 mg BID, exposure and an elimination half-life of approximately 1 hour were relatively comparable across most individuals in healthy subject and patient studies. Variability in exposure to acalabrutinib is mainly due to a combination of pH-dependent dissolution and absorption and predominantly CYP3A-mediated metabolism.

Acalabrutinib is extensively and nearly completely metabolized by three major pathways. The most abundant circulating metabolite in human was ACP-5862 (denoted M27) which was formed by CYP3A and also circulated in nonclinical species. A PBPK model incorporating acalabrutinib and active metabolite ACP-5862 (M27) BTK binding kinetics, plasma protein binding and clinical PK indicated that ACP-5862 may contribute to BTK target coverage.

Therapeutic plasma acalabrutinib concentrations after a 100-mg dose or supratherapeutic plasma acalabrutinib concentrations after a 400-mg dose in healthy subjects did not prolong the QTc interval in a thorough QT study.

The 100 mg BID dose and schedule was selected for most oncologic indications because it results in continuous near-saturation BTK target coverage with the least inter-subject variability and an acceptable safety profile.

Further details can be found in the latest version of the investigator brochure.

2.2.3.4 Drug-drug Interaction Potential

At the systemic exposure levels expected in this study, acalabrutinib inhibition of CYP metabolism is not anticipated. However, acalabrutinib is metabolized by CYP3A. Concomitant administration of acalabrutinib with a strong CYP3A inhibitor, itraconazole increased exposure by approximately 5-fold. Additionally, concomitant administration of acalabrutinib with moderate CYP3A inhibitors, fluconazole and isavuconazole, increased exposure by approximately ≤2-fold. Conversely, concomitant administration of acalabrutinib with a strong CYP3A inducer, rifampin decreases acalabrutinib exposure by 77%. Consequently, the concomitant use of strong inhibitors/inducers of CYP3A should be avoided when possible. Alternatively, if the strong inhibitor will be used short-term (such as anti-infectives for up to seven days), interrupt acalabrutinib. When acalabrutinib is administered with moderate CYP3A inhibitors, no dose adjustment is needed but monitor patients closely for adverse reactions. If a strong CYP3A inducer cannot be avoided, increase the acalabrutinib dose to 200 mg twice daily. See Appendix E for a list of strong CYP3A inhibitors/inducers.

The effect of agents that reduce gastric acidity (antacids or proton-pump inhibitors) on acalabrutinib absorption was evaluated in a healthy volunteer study (ACE-HV-004). Results from this study indicate that subjects should avoid the use of calcium carbonate-containing drugs or supplements for a period of 2 hours before and at least 2 hours after taking acalabrutinib. Use of omeprazole, esomeprazole, lansoprazole or any other proton-pump inhibitors while taking acalabrutinib is not recommended due to a potential decrease in study drug exposure. However, the decision to treat with proton-pump inhibitors during the study is at the investigator's discretion, with an understanding of the potential benefit to the subject's gastrointestinal condition and a potential risk of decreased exposure to acalabrutinib.

If treatment with an H2-receptor antagonist is required, the H2-receptor antagonist should be taken approximately 2 hours after an acalabrutinib dose.

For more detailed information on drug-drug interaction potential for acalabrutinib, refer to the Investigator Brochure.

2.2.3.5 Clinical Experience

As of 03 September 2017, acalabrutinib has been administered to >2000 participants in clinical studies, including subjects with hematologic malignancies, solid tumor, or rheumatoid arthritis, and participants who are healthy volunteers or with mild to moderate hepatic impairment. For more detailed information on the clinical experience for acalabrutinib, please refer to the Investigator Brochure.

This section briefly summarizes data from ACE-CL-001 (clinicaltrials.gov; #NCT02029443), an ongoing nonrandomized, sequential group, dose-escalation Phase 1/2 study in subjects with R/R or previously untreated chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), Richter's syndrome, or prolymphocytic leukemia. Efficacy data as of 03 April 2017 have been evaluated for subjects with chronic lymphocytic leukemia (CLL), including subjects with relapsed/refractory (R/R) CLL (N=134), treatment-naive subjects (N=99), ibrutinib-intolerant subjects (N=33), and subjects with Richter's syndrome or prolymphocytic leukemia (PLL) transformation (N=29). Tumor response was based on International Working Group response criteria (Hallek 2008) as updated (Cheson 2012) to include partial response (PR) with treatment-induced lymphocytosis (PRL). Median time on study for the R/R, treatment-naive, ibrutinib-intolerant and Richter's syndrome populations, respectively, was 24.5, 24.8, 19.0 and 2.8 months. Overall response rate (ORR) for the 4 populations was 96.9%, 99.0%, 80.6%, and 37.0%, respectively. For more detailed information and updates, please refer to the current Investigator Brochure.

A Phase 2 study of acalabrutinib monotherapy (100 mg BID) in subjects with R/R MCL is currently ongoing (ACE-LY-004; clinicaltrials.gov: NCT02213926). As of 28 February 2017, 124 subjects were enrolled and received at least 1 dose of acalabrutinib. Acalabrutinib appears to be well tolerated with evidence of efficacy in this population. All 124 subjects were

evaluable for efficacy with a median duration on study of 15.2 months (range: 0.3 to 23.7 months). The ORR (CR + PR) by investigator's assessment according to the 2014 Lugano classification was 80.6% (95% CI: 72.6%, 87.2%) with a CR rate of 40% (refer to current Investigator Brochure).

On 31 October 2017, the United States (US) Food and Drug Administration (FDA) granted accelerated approval for acalabrutinib (Calquence®) for treatment of adult patients with MCL who have received at least one prior therapy based on pivotal Study ACE-LY-004.

2.3 Benefit/risk assessment

2.3.1 Overall Benefit/risk assessment

This is the first study designed to evaluate the safety, tolerability and pharmacokinetics of the BTK inhibitor, acalabrutinib, in Chinese adult subjects with advanced B-cell malignancies. Acalabrutinib may have the potential to provide benefit in patients with advanced B cell malignancy.

As of 03 September 2017, acalabrutinib has been administered to over 2000 participants in clinical studies, including subjects with hematologic malignancies, solid tumors, or rheumatoid arthritis, and participants who are healthy subjects or those with mild to moderate hepatic impairment. Hemorrhage is an important identified risk. Important potential risks are infections, cytopenias, second primary malignancies and atrial fibrillation.

Both ACE-CL-001 and ACE-LY-004 represent efficacy data for acalabrutinib monotherapy. In subjects with relapsed/refractory (R/R) CLL (N=134), treatment-naive subjects (N=99), ibrutinib-intolerant subjects (N=33), and subjects with Richter's syndrome or prolymphocytic leukemia (PLL) transformation (N=29). Overall response rate (ORR) for the 4 populations was 96.9%, 99.0%, 80.6%, and 37.0%, respectively. In ACE-LY-004, all 124 subjects were evaluable for efficacy with a median duration on study of 15.2 months (range: 0.3 to 23.7 months). The ORR (CR + PR) by investigator's assessment according to the 2014 Lugano classification was 80.6% (95% CI: 72.6%, 87.2%) with a CR rate of 40% (refer to current Investigator Brochure). Please refer to 2.2.3.5.

The proposed Chinese Phase 1/2 trial will characterize the safety of acalabrutinib in B-cell malignancies. The proposed exclusion criteria, safety monitoring, starting dose, and stopping criteria will minimize the risks for the subjects participating in this study. The preliminary data suggest that acalabrutinib is well tolerated and has activity as a single agent in R/R MCL and R/R CLL. Based on available data, the risk/benefit for acalabrutinib is considered acceptable for the proposed clinical study.

More detailed information about the known and expected benefits and potential risks of acalabrutinib may be found in the Investigator's Brochure and Development Safety Update Report (DSUR).

2.3.2 Risks Associated with Acalabrutinib Treatment

2.3.2.1 Contraindications

No contraindications are known for acalabrutinib.

2.3.2.2 Important Identified Risks

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

Hemorrhage

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

The mechanism for hemorrhage is not well understood. Subjects receiving antithrombic 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.

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

Infections

Serious infections (bacterial, viral, and fungal) including fatal events, have occurred in clinical studies with acalabrutinib. The most frequently reported Grade ≥ 3 infection was pneumonia (preferred term). Across the acalabrutinib clinical development program (including subjects treated with acalabrutinib in combination with other drugs), cases of hepatitis B virus (HBV) reactivation, aspergillosis, and progressive multifocal leukoencephalopathy (PML) have occurred.

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

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

Cytopenias

Treatment - emergent Grade 3 or 4 cytopenias including neutropenia, anemia, and thrombocytopenia have occurred in clinical studies with acalabrutinib. Monitor blood counts as medically appropriate. Please refer to 6.6.2 for study drug modification guidance.

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

Second Primary Malignancies

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

Subjects should be monitored for signs and symptoms of malignancy. Subjects 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 patients to permanently discontinue study treatment. Continuation of acalabrutinib treatment should be discussed with the medical monitor.

Atrial Fibrillation

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 clinically indicated. Subjects with atrial fibrillation should be managed per institutional guidelines with supportive care and diagnostic evaluations as clinically indicated.

2.3.2.3 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 Investigator's Brochure.

Hepatotoxicity

The mechanism underlying hepatotoxicity events of non-infectious etiology is currently unknown. Following a comprehensive review of hepatotoxicity events in the acalabrutinib clinical program, there was insufficient evidence to establish an association between hepatotoxicity events and acalabrutinib due to the contribution of confounding factors, absence of clinical symptoms, and quick recovery without treatment for patients with

transaminase elevations. There is limited evidence regarding hepatotoxicity of non-infectious etiology from literature for other BTK inhibitors.

3. OBJECTIVES AND ENDPOINTS

Table 4 Study objectives

Phase 1 Portion - Primary Objective:	**Endpoint/Variable:**
To assess the safety and tolerability of acalabrutinib in Chinese subjects with R/R B-cell malignancies	AEs, laboratory data, vital signs, and ECGs
CCI [redacted]	CCI [redacted]
Phase 1 Portion - Secondary Objective:	**Endpoint/Variable:**
To assess the efficacy of acalabrutinib in Chinese subjects with R/R B-cell malignancies	For R/R CLL: Tumor response (number of patients with CR, CRi, PR, nPR, PRL, SD, PD) For other R/R B-cell malignancies: Tumor response (number of patients with CR, PR, SD, PD)
Phase 2 Portion Cohort A - Primary Objective:	**Endpoint/Variable:**
To assess the efficacy of acalabrutinib in Chinese subjects with R/R MCL	ORR as assessed by BICR per Lugano classification for NHL (Cheson 2014)
Phase 2 Portion Cohort A- Secondary Objective:	**Endpoint/Variable:**
To further assess the efficacy of acalabrutinib in Chinese subjects with R/R MCL	DoR, PFS and TTR as assessed by BICR per Lugano classification for NHL (Cheson 2014); ORR, DoR, PFS and TTR as assessed by investigators per Lugano classification for NHL (Cheson 2014); OS
To assess the safety profile of acalabrutinib in Chinese subjects with R/R MCL	AEs, laboratory parameters, vital signs, and ECGs
To assess pharmacokinetics of acalabrutinib in Chinese subjects with R/R MCL	Plasma concentration of acalabrutinib (sparse sampling)
Phase 2 Portion Cohort B- Primary Objective:	**Endpoint/Variable:**
To assess the efficacy of acalabrutinib in Chinese subjects with R/R CLL	ORR as assessed by BICR per iwCLL 2018 criteria

Table 4 Study objectives

Phase 2 Portion Cohort B- Secondary Objective:	Endpoint/Variable:
To further assess the efficacy of acalabrutinib in Chinese subjects with R/R CLL	DoR, PFS and TTR as assessed by BICR per iwCLL 2018 criteria; ORR, DoR, PFS and TTR as assessed by investigators per iwCLL 2018 criteria; TTNT; Minimal residual disease negative rate (defined as the proportion of subjects with MRD-negativity) measured in the peripheral blood by flow cytometry; OS
To assess the safety profile of acalabrutinib in Chinese subjects with R/R CLL	AEs, laboratory parameters, vital signs, and ECGs
To assess pharmacokinetics of acalabrutinib in Chinese subjects with R/R CLL	Plasma concentration of acalabrutinib (sparse sampling)
Safety Objectives are contained within the primary and secondary objectives.	

Data from R/R MCL subjects in both Phase 1 and Phase 2 will be combined for analysis.

4. STUDY DESIGN

4.1 Overall design

This is an open-label, two-part study to assess the safety, tolerability, pharmacokinetics and clinical efficacy of acalabrutinib in Chinese adult subjects with R/R MCL, R/R CLL and other B-cell malignancies. The study is divided into 2 parts: Phase 1 portion and Phase 2 portion.

Phase 1 portion

The primary objective of Phase 1 portion is to assess the safety, tolerability and pharmacokinetics of acalabrutinib in Chinese subjects with R/R B-cell Malignancies and the secondary objective is to access the efficacy of acalabrutinib in Chinese subjects with R/R B-cell malignancies. Approximately 12 subjects will be enrolled in the Phase 1 portion including subjects with R/R non-GCB diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL), Small Lymphocytic Lymphoma (SLL).

Subjects will be administered a single dose of acalabrutinib 100 mg at Cycle 0 Day 1. During the following 2 days wash-out period, intensive PK samples will be collected before and after the first dose until pre-dose at Cycle 1 Day 1. From Cycle 1 Day 1, subjects will be administered multiple doses of acalabrutinib 100 mg BID on a continuous schedule (28 days per cycle). Intensive PK samples will be collected on Cycle 1 Day 8 for 12-hour PK profile at steady state. Additional sparse PK samples will be collected on Cycle 1 Day 28 to assess time-dependent changes. Treatment with acalabrutinib may be continued for Cycle 2 onwards until

disease progression or any other treatment discontinuation criterion is met. All subjects who discontinue the study drug will have a safety follow-up visit 30 (+7) days after the last dose of study drug.

The dose regimen of multiple doses of 100 mg BID has been found to be safe/tolerable and potentially effective in overseas clinical studies in Western and Asian subjects. In case of intolerable toxicity, dose reduction to 100 mg QD may be considered (details in Section 6.6.2). Subjects will continue on treatment with acalabrutinib until a treatment discontinuation criterion is met.

Phase 2 portion

Phase 2 portion is to further evaluate clinical efficacy, safety and tolerability in subjects with R/R MCL and R/R CLL. Evaluation of efficacy and safety will be performed independently for each cohort.

Cohort A

Cohort A is to evaluate clinical efficacy, safety and tolerability in subjects with pathologically documented MCL who have relapsed after, or were refractory to, ≥1 (but not >5) prior treatment regimens. Approximately 33 R/R MCL subjects will be enrolled to receive 100 mg of acalabrutinib BID in repeated 28-day cycles.

Cohort B

Cohort B is to evaluate clinical efficacy, safety and tolerability in subjects with CLL who have failed from ≥ 1 prior systemic therapies. Approximately 60 R/R CLL subjects will be enrolled to receive 100 mg of acalabrutinib BID in repeated 28-day cycles.

Treatment with acalabrutinib may be continued until disease progression or any other treatment discontinuation criterion is met. Dose modification provisions are outlined in Section 6.6.2. Note: Temporary withholding of study drug for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. Refer to Section 7.1 for more information on assessing disease progression under these circumstances. An early termination visit is required for any subjects who permanently discontinue study drug for any reason (except for death, lost to follow up or withdrawal of consent), including disease progression. In addition to the early termination visit, all subjects who discontinue study drug will have a safety follow-up visit 30 (+ 7) days after his or her last dose of study drug.

All subjects will have hematology, clinical chemistry, and urinalysis safety panels done at screening. Once dosing commences (Cycle 1 Day 1), all subjects will be evaluated for safety, including hematology and clinical chemistry at regular basis.

Tumor assessments for R/R MCL subjects will be performed at 8- to 12-week intervals throughout the study. Tumor assessments for R/R CLL subjects will be performed at 12- to 24-week intervals throughout the study. Refer to Section 1.1 for a comprehensive list of study assessments and their timing. The end of trial is defined as the 3rd analyses for R/R CLL subjects of Phase 2 cohort B, which will occur approximately 24 months after the last R/R CLL subject enrolled into Phase 2.

The primary efficacy analyses (R/R MCL and R/R CLL subjects) will be based on Blinded Independent Central Review (BICR) assessment.

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

The guidance given below 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 [SARS-CoV-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 plans below 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. Where allowable by local health authorities, ethics committees, health care provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

- Obtaining consent/reconsent for the mitigation procedures (note, in the case of verbal consent/reconsent, the informed consent form (ICF) should be signed at the participant's next contact with the study site).

- Telemedicine visit: Remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix F

4.2 CCI [redacted]

tolerability and PK data of acalabrutinib in in Chinese population. The study population of CCI [redacted]

4.3 Justification for dose

The recommended dose of acalabrutinib is 100 mg BID based on the following data:

In the Phase 1/2 study in subjects with CLL/SLL (ACE-CL-001), subjects have received acalabrutinib at dosages from 100 mg QD to 400 mg QD or 100 mg to 200 mg BID. No dose-limiting toxicities (DLTs) were identified at dosages of ≤ 400 mg once per day (QD) or 100 to 200 mg BID. With a median follow up of 15.5 months in evaluable subjects (n=128), the best overall response rate, including partial response and partial response with lymphocytosis (PR+L), was 96.9%.

Pharmacodynamics results from ACE-CL-001 suggest BTK resynthesis occurs in malignant B cells within 24 hours. While all dosages evaluated show full BTK occupancy 4 hours after dosing, the 100 mg BID cohort shows full target coverage over 24 hours (≥ 97% BTK occupancy at 4 and 24 hours). Based on pharmacokinetics/pharmacodynamics and efficacy results of the Phase 1/2 study, acalabrutinib 100 mg BID is selected as the recommended dose.

In a multicenter, open-label Phase 2 Study (ACE-LY-004) in subjects with R/R MCL, Acalabrutinib 100 mg BID monotherapy was generally well tolerated and resulted in a high ORR and CR rate, with responses that were durable and clinically meaningful. Please refer to Section 2.2.3.5.

In an ongoing Japanese Phase 1 study (D8220C00001), preliminary data from Part 1 (the dose-confirmation phase) showed acceptable safety and tolerability profiles. No DLTs was observed among the 6 evaluable subjects. No clinical relevant PK ethnic difference was observed between Japanese and Western subjects.

4.4 End of study definition

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 pre-specified protocol or is terminated.

For this study, the study will end at the time of the 3rd analyses for R/R CLL subject of Phase 2 cohort B, which is anticipated to occur approximately 24 months after the last R/R CLL subject enrolled in Phase 2.

There will be 2 data cut-offs defined after the last patient enrolled at cohort A, and 3 data cut-offs defined after the last patient enrolled at cohort B (Section 9.4). Data analysis will be performed, and a Clinical Study Report will be written based on each data set at the timing of the 1st data cut-off as defined in Section 9.4. Clinical Study Report Addendums will be prepared at the 2nd data cut-off of cohort A and the 2nd & 3rd data cut-off of cohort B.

Any subjects still receiving investigational product at the time of the 2nd data cut-off of phase I and cohort A and the 3rd data cut-off of cohort B will be able to continue to receive acalabrutinib while deriving clinical benefit and not meet the discontinuation criteria. For such subjects, with exception of paper-base SAEs, no data after final DCO and electronic database closure (2nd DCO for phase I and cohort A participants; 3rd DCO for cohort B participants) would be collected for the purpose of this study. Investigators will continue to report all SAEs to AstraZeneca Patient Safety until 30 days after the last dose of study treatment or the start of new anticancer therapy (whichever comes first), in accordance with Section 8.4.1 (Reporting of serious adverse events). Additionally, as stated in Section 8.3.3 (Follow-up of AEs and SAEs), any SAE or non-serious AE that is ongoing at the time defined as the end of the study must be followed up to resolution, stabilization, unless the event is considered by the Investigator to be unlikely to resolve, or the subject is lost to follow-up. In addition, after each cohort final data cut-off, it is not necessary to submit the sample to the central laboratory.

In the event that a roll-over or safety extension study is available at the time of the study closure, subjects who are still on treatment at the end of the study and deriving clinical benefit from acalabrutinib treatment may be eligible to enroll in a separate rollover study.

See Section 6.7 for detail information for treatment after the end of study. See Appendix A6 for guidelines for the dissemination of study results.

5. STUDY POPULATION

In this protocol, subjects who sign informed consent will undergo screening according to inclusion and exclusion criteria.

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be assigned to a study intervention. Under no circumstances can there be exceptions to this rule. Subjects who signed a consent form but do not meet the entry requirements are screen failures, refer to Section 5.4.

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted. Subjects will be enrolled in China. In phase 1 portion, the study population includes subjects with R/R non-GCB DLBCL, FL, MCL, CLL/ SLL. Phase 2 portion cohort A will enroll MCL subjects who have relapsed after or were refractory to ≥1 (but not >5) prior treatment regimens. Phase 2 portion cohort B will enroll CLL subjects who failed from ≥1 prior systemic therapies.

For procedures for withdrawal of incorrectly enrolled subjects see Section 7.3.

5.1 Inclusion criteria

Subjects are eligible to be included in the study only if all of the following inclusion criteria and none of the exclusion criteria apply:

Informed consent

1 Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

2 Provision of signed and dated, written informed consent form prior to any mandatory study specific procedures, sampling, and analyses.

The ICF process is described in Appendix A3.

Age

3 Chinese subjects at least 18 years of age at the time of study entry.

Type of subject and disease characteristics

4 Eastern Cooperative Oncology Group (ECOG) performance status of ≤2

5 Have a life expectancy of at least 3 months

6 Adequate hematological function defined as: absolute neutrophil count (ANC) ≥0.75 × 10^9/L and platelet count ≥50 ×10^9/L. For subjects with disease involvement in the bone marrow, ANC ≥0.50 × 10^9/L and platelet count ≥30 × 10^9/L. Subject must be without growth factor support and platelet transfusion support 7 days before assessment.

7 Adequate organ function defined as follows: aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2 × ULN, total bilirubin ≤1.5 × ULN except in the case of subjects with documented Gilbert's disease, ≤2.5 × ULN. Estimated creatinine clearance of ≥50 mL/min, calculated using the formula of Cockcroft and Gault [(140-age) • mass (kg)/ (72 • creatinine mg/dL) • multiply by 0.85 if female]

8 Presence of radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (for NHL: have ≥1 nodal lesion >2.0 cm in the longest diameter, and/or

extranodal lesion >1.0 cm in the longest diameter; for CLL: have ≥1 nodal lesion >2.0 cm in the longest diameter as assessed by computed tomography scan).

9 For subjects in Phase 1 portion, subjects should accept hospitalization at least from Cycle 0 Day -1 to Cycle 0 Day 2. Then, each subject may be discharged at an appropriate point on or after Cycle 0 Day 2 at the discretion of the investigator based on the result of assessment at discharge, which is the same as the test items performed at each pre-defined visit.

Inclusion criteria for MCLs in Phase 1 and Phase 2 portion Cohort A

10 Pathologically confirmed MCL, with documentation of chromosome translocation t (11;14) (q13; q32) and/or overexpression of cyclin D1 in association with other relevant markers (e.g., CD5, CD19, CD20, PAX5). Pathology report should be reviewed by study physician to confirm eligibility.

11 Disease had relapsed after or been refractory to ≥1 but no more than 5 prior therapy for MCL and now subjects require further treatment.

12 Documented failure to achieve at least partial response (PR) with, or documented disease progression after, the most recent treatment regimen.

Inclusion criteria for CLL in Phase 1 and Phase 2 portion Cohort B

13 Diagnosis of CLL that meets published diagnostic criteria (Hallek 2018)

(a) Monoclonal B-cells (either kappa or lambda light chain restricted) that are clonally co-expressing ≥ 1 B-cell marker (CD19, CD20, or CD23) and CD5.

(b) Prolymphocytes **may** comprise <55% of blood lymphocytes.

(c) Presence of $\geq 5*10^9$ B lymphocytes/L (5000/uL) in the peripheral blood (at any point since the initial diagnosis)

14 Must have received ≥ 1 prior systemic therapies for CLL. Note: Single-agent steroids or localized radiation are not considered a prior line of therapy. If a single-agent anti-CD20 antibody was previously administered, subjects must have received ≥ 2 doses.

15 Documented failure to achieve at least partial response (PR) or documented disease progression after response to the most recent treatment regimen.

16 Active disease per iwCLL 2018 criteria that requires treatment, at least 1 of the following criteria should be met

(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/μL)

(b) Massive (i.e., ≥6 cm below the left costal margin), progressive, or symptomatic splenomegaly

(c) Massive nodes (i.e., ≥10 cm in the longest diameter), progressive, or symptomatic lymphadenopathy

(d) Progressive lymphocytosis with an increase of >50% over a 2-month period or a lymphocyte doubling time (LDT) of <6 months. LDT may be obtained by linear regression extrapolation of ALC obtained at intervals of 2 weeks over an observation period of 2 to 3 months. In subjects with initial blood lymphocyte counts of $<30x10^9$/L (30,000/μL), LDT should not be used as a single parameter to define indication for treatment. In addition, factors contributing to lymphocytosis or lymphadenopathy other than CLL (e.g., infections) should be excluded.

(e) Autoimmune anemia and/or thrombocytopenia that is poorly responsive to standard therapy

(f) B-symptoms documented in the subject's chart with supportive objective measures, as appropriate, defined as ≥1 of the following disease-related symptoms or signs:

(i) Unintentional weight loss ≥10% within the previous 6 months before Screening

(ii) Significant fatigue (ECOG performance status 2 or higher; inability to work or perform usual activities)

(iii) Fevers higher than 100.5°F or 38.0°C for ≥2 weeks before Screening without evidence of infection

(iv) Night sweats for ≥1 month before Screening without evidence of infection

Inclusion criteria for all other B-cell malignancies in Phase 1 portion

17 Documented diagnosis of non-GCB DLBCL or indolent non-Hodgkin lymphoma (iNHL) (FL, SLL) by medical records and with histology based on criteria established.

(a) For non-GCB DLBCL, follow Hans algorithm (Hans 2004).

(b) For iNHL, following criteria are required:

(i) The histology shows FL Grade 1,2 or 3a or SLL

(ii) Have disease that requires systemic treatment (For SLL, following International Workshop on Chronic Lymphocytic Leukaemia (iwCLL) 2018 criteria (Hallek 2018); For FL, investigator's discretion referring GELF criteria (Brice 1997))

18 No treatment option with generally accepted standard therapy.

Reproduction

19 Negative pregnancy test (urine or serum) for female subjects of childbearing potential prior to enrolment.

20 Female subjects of childbearing potential who are sexually active with a non-sterilized male partner must use highly effective contraception from screening through 2 days after the last dose of acalabrutinib. A highly effective method of contraception is defined as Table 5. Females subjects not of childbearing potential must have been surgically

sterilized (e.g., hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or postmenopausal (defined as at least 1 year since last regular menses in absence of other medical reasons for amenorrhea, including treatment with drugs such as anticancer agents).

Table 5 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 (IUD) or intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion • Vasectomy of a female subject'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 treatments) 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 treatments as the subject's preferred and usual lifestyle. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, and post-ovulation methods) and withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together as an effective method of contraception.

5.2 Exclusion criteria

Medical conditions

1 Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject had been disease free for ≥2 years or which would not have limited survival to <2 years. Note: These cases must have been discussed with the study physician.

2 A life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could have compromised the subject's safety, interfered with the absorption or metabolism of acalabrutinib, or put the study outcomes at undue risk.

3 Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of Screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification.

4 Significant screening electrocardiogram (ECG) abnormalities including left bundle branch block, 2nd degree AV block type II, 3rd-degree AV block, Grade ≥2 bradycardia, or average QT interval corrected for heart rate (QTc) from the three screening ECGs >480 msec (calculated using Fridericia's formula: $QT/RR^{0.33}$)

5 Malabsorption syndrome, disease significantly affecting gastrointestinal (GI) function, or resection of the stomach or small bowel, gastric bypass, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.

6 Known central nervous system involvement of lymphoma/leukemia or leptomeningeal disease.

7 Known history of HIV, serologic status reflecting active hepatitis B or C infection, or any uncontrolled active systemic infection.

- Subjects who are hepatitis B core antibody (anti-HBc) positive and surface antigen (HBsAg) negative will need to have a negative HBV DNA polymerase chain reaction (PCR) result before enrolment. Those who are hepatitis B surface antigen (HBsAg) positive or hepatitis B PCR positive will be excluded.
- Subjects who are hepatitis C antibody positive will need to have a negative HCV RNA PCR result before enrolment. Those who are hepatitis C PCR positive will be excluded.

8 Major surgery within 4 weeks before first dose of study drugs. Note: If a subject had major surgery, they must have recovered adequately from any toxicity and/or complications from the intervention before the first dose of study drug.

9 Ongoing drug-induced pneumonitis.

10 Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura.

11 Known history of a bleeding diathesis (e.g., hemophilia, von Willebrand disease).

12 History of stroke or intracranial hemorrhage within 6 months before the first dose of study treatment.

13 Known prolymphocytic leukemia or history of, or currently suspected, Richter's syndrome (for CLL/SLL)

14 Presence of a GI tract ulcer diagnosed by endoscopy within 3 months prior to screening

15 Uncontrolled active systemic fungal, bacterial, viral, or other infection (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment) or ongoing intravenous anti-infective treatment.

16 Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥2 toxicity (other than alopecia, neutropenia and thrombocytopenia outlined in Inclusion criteria #6) continuing from prior anticancer therapy including radiation.

Prior/concomitant therapy

17 Required or received anticoagulation with warfarin or equivalent vitamin K antagonist (e.g., phenprocoumon) within 7 days of first dose of study treatment.

18 Requires treatment with proton pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole or rabeprazole). Subjects receiving proton pump inhibitors who switch to H2-receptor antagonists or antacids are eligible for enrollment to this study.

19 Receipt of any biological or immunological based therapies (including experimental therapies) for leukaemia or lymphoma or myeloma (including, but not limited to, MAb therapy such as rituximab, or cancer vaccine therapies) within 4 weeks prior to the first dose of acalabrutinib.

20 The time from the last dose of the most recent chemotherapy or experimental therapy to the first dose of study treatment was <5 times the half-life of the previously administered agent(s).

21 Prior exposure to a BCR inhibitor (e.g., BTK, phosphoinositide-3 kinase [PI3K], or SYK inhibitors) or BCL-2 inhibitor (e.g., venetoclax).

22 Prior allogeneic stem cell transplant.

23 Ongoing immunosuppressive therapy, including systemic (e.g., IV or oral) corticosteroids of underlying disease within 2 weeks before the first dose of study drug. Note: Subjects may use topical or inhaled corticosteroids or steroids (≤20 mg prednisone equivalent/day for ≤2 weeks) as a therapy for comorbid conditions. During study participation, subjects may also receive systemic (e.g., IV or oral) corticosteroids as needed for treatment-emergent comorbid conditions.

24 Use of a strong inhibitor or inducer of CYP3A within 7 days before dose of study drug or expected requirement for use of a CYP3A inhibitor or inducer (including herbal medication known to modulate CYP3A4 enzyme activity) during the first 28 days of administration of study drugs.

25 Received a live virus vaccination within 28 days of first dose of study drug.

26 History of allergy or hypersensitivity to any component of the acalabrutinib formulation

Prior/concurrent clinical study experience

27 Concurrent participation in another therapeutic clinical trial.

Other exclusions

28 Breastfeeding or pregnant (breastfeeding is not allowed during treatment and until 2 days after the end of treatment. However, resumption of breastfeeding 2 days after the last dose is allowed.)

29 Judgment by the investigator that the subject should not participate in the study if the subject is unlikely to comply with study procedures, restrictions and requirements.

5.3 Lifestyle restrictions

The following restrictions apply while the subject is receiving study treatment and for the specified times before and after:

1 Females of child-bearing potential should use highly effective methods of contraception (see Table 5) from the time of screening until 2 days after discontinuing acalabrutinib.
2 Acalabrutinib is best taken with water and can be taken with or without food. As acalabrutinib are metabolized by CYP3A, subjects should be strongly cautioned against the use of herbal medication or dietary supplements (in particular, St John's wort, which is a potent CYP3A inducer).
3 Otherwise, subjects should maintain their regular diet unless modifications are required to manage an AE such as diarrhoea, nausea, or vomiting.
4 Smoking and alcohol intake will be monitored during intensive PK sampling period of Phase 1 portion.

For restrictions relating to concomitant medications see Section 6.5.2.

5.4 Screen failures

Screen failures are defined as subjects who signed the informed consent form to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

These subjects should have the reason for study withdrawal recorded in the electronic CRF (i.e., subject does not meet the required inclusion/exclusion criteria).

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened one more time which requires signing the ICF again and repeating screening procedures. Investigator should discuss individual case with study physician before patient is rescreened. The bone marrow biopsy and aspirate, CT and PET-CT scan do not need to be repeated if still within timeframe prior to the first dose as required in protocol. Subjects that re-screen must be re-entered in IXRS and will receive a new Subject ID.

6. STUDY TREATMENTS

Study treatment is defined as any investigational product(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study

participant according to the study protocol. Study treatment in this study refers to Acalabrutinib.

6.1 Treatments administered

6.1.1 Investigational products

Investigational product	Dosage form and strength	Manufacturer
Acalabrutinib	100 mg, opaque size 1 hard capsule with a yellow and blue	CCI [redacted]

Acalabrutinib is intended to be administered orally once or twice daily with approximately 240 mL of water. Acalabrutinib may be taken with or without food. Acalabrutinib should be taken under fasting condition (at least 10 hours before dosing and at least 4 hours after dosing) in the Phase 1 portion morning dose of Cycle 0 Day 1 and Cycle 1 Day 8. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in liquid. Doses should be administrated approximately 12 hours apart, it is recommended that acalabrutinib 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 subject 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.

The investigational product, acalabrutinib capsules for oral administration, is supplied as blue and yellow opaque hard gelatinous capsules and is provided in white, high-density polyethylene bottles. Additional information about the investigational product may be found in the Investigator Brochure.

Labels will be prepared in accordance with Good Clinical Practice (GCP) Ordinance. All study drugs should be kept in a secure place under appropriate storage conditions. A description of the appropriate storage conditions is specified in the labels.

6.1.2 Duration of therapy

Subjects may continue to receive acalabrutinib until meet the discontinuation criteria (Section 7.1). Safety follow-up assessments will be conducted at 30 days (+7 days) post last dose of therapy.

Subjects who discontinue study therapy due to reasons other than disease progression will continue on study for post-treatment disease follow up and subjects who have disease progression will be followed for survival (see Section 7.1.2) unless they withdraw consent or loss to follow up.

6.2 Preparation/handling/storage/accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.

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

The unused study treatment will be returned to AstraZeneca for disposition.

6.3 Measures to minimize bias: randomization and blinding

There will be no randomization scheme in this study. All subjects across Phase 1 and Phase 2 will be assigned to receive acalabrutinib. This is an open-label study, methods for ensuring blinding is not applicable.

6.4 Treatment compliance

For acalabrutinib taken in the clinic, subjects should take the dose from the drug dispensed to them for that particular time period. All other study treatments will be taken at home. Subjects will receive a drug diary to record the specific time each dose was taken and to record reasons for any missed doses.

Subject compliance will be assessed at each study visit. The subject will be instructed to bring the diary and any remaining capsules to the clinic at their next visit. The study staff will review the diary and ask the subject if all of the capsules were administered. Any remaining or returned capsules will be counted and recorded in accountability records as described in Section 6.2. Returned capsules must not be redispensed to another subject.

The investigational product should only be used as directed in this protocol. Details of treatment with investigational product including: change from the dosing schedule, does interruptions, dose reductions, dose discontinuations should be recorded in eCRF.

The investigational product will not be distributed to the study site until the contract is concluded between the study site and AstraZeneca. The investigator or designee is responsible for managing the IMP from receipt by the study site until the return of all unused IMP to

AstraZeneca. The Investigator(s) is responsible for ensuring that the subject has returned all unused IMP.

6.5 Concomitant therapy

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal medication that the subject is receiving at the time of 4 weeks prior to starting study treatment and all concomitant treatments during the study must be recorded in the Electronic Case Report Form (eCRF) along with:

- Reason for use (Indication)
- Dates of administration including start and end dates
- Dosage information including dose, frequency and route

6.5.1 Permitted concomitant therapy

- Permitted concomitant therapy is acceptable during study treatment. Antiemetics are permitted if clinically indicated. Standard supportive care medications are permitted as per institutional standards. Use of hematopoietic growth factors is permitted per Consensus of Chinese Experts (Version 2015). (Primary prophylactic use of myeloid growth factors (e.g., granulocyte colony-stimulating factor [G-CSF]) is not allowed according to the guideline.)
- For subjects considered at risk for tumor lysis syndrome: Administer appropriate hydration and allopurinol or rasburicase per institutional standards before initiating treatment.
- Prophylaxis for bacterial/viral/fungal is allowed per institutional standards.
- During study participation, subjects may receive systemic or enteric corticosteroids at any required dosage as needed for treatment-emergent comorbid conditions such as treatment emergent colitis or pneumonitis.

6.5.2 Prohibited concomitant therapy

Any concurrent chemotherapy (e.g., bendamustine, cyclophosphamide, pentostatin, or fludarabine), anticancer immunotherapy (e.g., rituximab, obinutuzumab, alemtuzumab, or ofatumumab), corticosteroids (at dosages equivalent to prednisone >20 mg/day), kinase inhibitors (e.g., ibrutinib, zanubrutinib and idelalisib), bone marrow transplant, experimental therapy, and radiotherapy are prohibited.

Warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon) are prohibited. Any herbal medication is prohibited from Cycle 0 Day 1 to Cycle 1 Day 8 (intensive PK sampling period) in Phase 1 portion. Administration of herbal medication during other treatment period is not recommended, unless it is prescribed by the investigator for treatment of specific clinical events. At study entry, subjects may be using topical or inhaled corticosteroids or

steroids (≤20 mg of prednisone or equivalent per day) as therapy for comorbid conditions but use of corticosteroids as therapy of the lymphoid cancer is not permitted.

Immunization with a live virus vaccine is prohibited within 28 days before study treatment and during study treatment.

The effect of agents that reduce gastric acidity (antacids or proton pump inhibitors) on acalabrutinib absorption was evaluated in a healthy volunteer study (ACE-HV-004). Results from this study indicate that subjects should avoid the use of calcium carbonate containing drugs or supplements for a period of at least 2 hours before and at least 2 hours after taking acalabrutinib. Use of omeprazole or esomeprazole or any other proton pump inhibitors while taking acalabrutinib is strongly not recommended due to a potential decrease in study drug exposure. If treatment with an H2-receptor antagonist is required, the H2-receptor antagonist should be taken approximately 2 hours after an acalabrutinib dose.

At the systemic exposure levels expected in this study, acalabrutinib inhibition of CYP metabolism is not anticipated. However, concomitant administration of acalabrutinib with a strong CYP3A inhibitor increased exposure by approximately 5-fold. Conversely concomitant administration of a strong inducer of CYP3A has the potential to decrease exposure of acalabrutinib and could reduce the efficacy of the study interventions. Consequently, the concomitant use of strong inhibitors/inducers of CYP3A (e.g. clarithromycin, itraconazole, carbamazepine and St John's wort) should be avoided when possible. Refer to Table 6 for Instruction for Coadministration of Drugs with Acalabrutinib Coadministered Drug.

Table 6 Instructions for Coadministration of Drugs with Acalabrutinib Coadministered Drug

Instructions for Coadministration of Drugs with Acalabrutinib Coadministered Drug	Acalabrutinib
Strong CYP3A inhibitor	Avoid concomitant use with acalabrutinib. If the inhibitor will be used short-term (such as anti-infectives for up to 7 days), interrupt acalabrutinib.
Moderate CYP3A inhibitor	No dose adjustment. Monitor patients closely for adverse reactions if taking moderate CYP3A inhibitors.
Strong CYP3A inducer	Avoid concomitant use. If a subject 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.

Instructions for Coadministration of Drugs with Acalabrutinib Coadministered Drug	Acalabrutinib
Moderate CYP3A inducer	No change
P-gp inhibitor	No change
BCRP inhibitor	No change
Narrow therapeutic index P-gp substrate	No change
Bile acid sequestrants	No change
Statin (OATP substrate)	No change
Proton pump inhibitors	Avoid concomitant use.
H2-receptor antagonists	Take acalabrutinib 2 hours before taking a H2-receptor antagonist.
Antacids	Separate dosing by at least 2 hours.

6.6 Dose delay and dose modification

6.6.1 Dose delay

Treatment with acalabrutinib should be held for any unmanageable, potentially study drug-related toxicity that is Grade ≥3 in severity. Any other clinically important events where dose delays may be considered appropriate by the investigator must be discussed with the sponsor. Study drug may be held for a maximum of 28 consecutive days from expected dose. Study treatment should be discontinued in the event of a toxicity requiring the postponement of dosing lasting >28 days, unless reviewed and approved by the sponsor.

Note: temporary withholding of study drug for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. Refer to Section 7.1 for more information on assessing disease progression under these circumstances.

6.6.2 Dose modification

The actions in Table 7 should be taken for the following toxicities (according to CTCAE criteria version 5.0 or higher):

- Grade 4 neutropenia (ANC< 500/μL) for > 7 days (Myeloid growth factors are permitted per Consensus of Chinese Experts (Version 2015) and use must be recorded on the eCRF).

- Grade 3 platelets decreases in the presence of clinically significant bleeding
- Grade 4 platelets decreases
- Grade 3 or 4 nausea, vomiting, or diarrhea, if persistent despite optimal antiemetic and/or anti-diarrheal therapy
- Any other Grade 4 toxicity or unmanageable Grade 3 toxicity.

If the toxicity resolves or reverts to ≤CTCAE grade 1 or baseline within 28 days of onset and the subject is showing clinical benefit, treatment with acalabrutinib may be restarted using the rules below for dose modifications (see Table 7). Whenever possible, any dose adjustment of acalabrutinib should be discussed between the investigator and the sponsor before implementation. The appropriate clinic staff should dispense the study drug for the new dose level and instruct the subject/caregiver about the change in dose level. Any changes to the dosing regimen must be recorded in the appropriate eCRF.

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 below. 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 7 Dose modifications for toxicity

Occurrence	Action
1st-2nd	Hold acalabrutinib until recovery to Grade ≤1 or baseline; may restart at original one-day dose level (100 mg BID)
3rd	For non-hematologic AEs, discontinue acalabrutinib. For thrombocytopenia with significant bleeding, discontinue acalabrutinib. For other hematologic AEs, upon recovery to Grade ≤1 or baseline, restart at 100 mg QD.
4th	For hematologic AEs, discontinue acalabrutinib.

6.7 Treatment after the end of the study

Any subjects still receiving investigational product at the time of the 2nd data cut-off of phase I and cohort A and the 3rd data cut-off of cohort B will be able to continue to receive acalabrutinib while deriving clinical benefit in the opinion of the Investigator, and not meet the discontinuation criteria. Administration of investigational product following final data cut-off will be recorded in site documents for supply management but will not be collected on the eCRF. It is recommended that investigators monitor the participant's safety laboratory results periodically during treatment with acalabrutinib in order to manage AEs, consistent with the dose modification guidelines for management of study intervention-related toxicities (see

Section 6.6). Such subjects will continue to be monitored for all AE up to 30 days after the last dose of investigational product.

In the event that a roll-over or safety extension study is available at the time of the study closure, subjects who are still on treatment at the end of the study and deriving clinical benefit from acalabrutinib treatment may be eligible to enroll in a separate rollover study. The roll-over or safety extension study would ensure treatment continuation with visit assessments per its protocol.

7. DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL

7.1 Discontinuation of study treatment

Subjects may be discontinued from investigational product in the following situations. Note that discontinuation from study treatment is NOT the same thing as a complete withdrawal from the study.

- Any subject who has objective evidence of disease progression while receiving protocol required study drug should be withdrawn from the study treatment. If there is uncertainty regarding whether there is disease progression, the subject may continue study treatment and remain under disease evaluation until confirmation of disease progression. In particular, transient worsening of disease during temporary interruption of study therapy (e.g., for drug-related toxicity, surgery, or intercurrent illness) may not indicate disease progression. In such circumstances, and if medically appropriate, subjects may resume therapy and relevant clinical, laboratory, and/or radiographic assessments should be done to document whether Tumor control can be maintained or whether actual disease progression has occurred.
- Any adverse event presents a substantial clinical risk to the subject with continued acalabrutinib dosing.
- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment.
- Pregnancy in a subject, intend to become pregnant or begin breast feeding.
- Severe non-compliance with the Clinical Study Protocol.
- Start of alternative anticancer therapy.
- Study terminated by Sponsor.

See the SoA (Section 1.1) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1 Procedures for discontinuation of study treatment

The investigator should instruct the subject to contact the site before or at the time if study treatment is stopped. A subject that decides to discontinue study treatment will always be

asked about the reason(s) and the presence of any AEs. The date of last intake of study treatment should be documented in the eCRF. All study treatment should be returned by the subject at their next on-site study visit or unscheduled visit. Subjects permanently discontinuing study treatment should be given locally available standard of care therapy, at the discretion of the Investigator.

Discontinuation of study treatment, for any reason, does not impact on the subject´s participation in the study. The subject should continue attending subsequent study visits and data collection should continue according to the study protocol.

The end of treatment visit should be performed within 7 days of the last dose of study drugs, if possible, and is not required for subjects who discontinue from study treatment within 10 days of a scheduled study visit or if the EoT visit would be performed within 14 days of the Safety Follow-up visit. 30 day (+ 7 days) safety follow-up visit is required for all subjects after his or her last dose of study drug to monitor for AEs, regardless of whether the subject receives a new anticancer therapy or demonstrates disease progression within this timeframe.

If the subject does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This could be a telephone contact with the subject at end of treatment follow up visit, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A subject that agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

7.1.2 Follow-up for progression and survival

Post-treatment Disease Follow up: All R/R MCL subjects enrolled in Phase 1 portion or subjects in Phase 2 portion and all R/R CLL subjects enrolled in Phase 2 portion who discontinue from study treatment due to reasons other than disease progression will be followed for disease evaluation approximately every 12 weeks or 24 weeks (± 7 days) from the latest date of disease evaluation before study treatment discontinuation until disease progression, regardless of whether the subject receives a new anticancer therapy. During this period, CT scans will be done approximately 12 weeks or 24 weeks.

Survival Follow up: R/R MCL subjects in Phase 1 or subjects in Phase 2 and R/R CLL subjects in Phase 2 who have disease progression, and have not withdrawn consent will be contacted approximately every 12 weeks by clinical visit or telephone, to assess survival and the use of alternative anticancer therapy until death or lost to follow up. At the time of the planned final analysis, a survival sweep may be conducted. All subjects who are on study and not known to have died before the survival sweep may be contacted at that time.

7.2 Lost to follow-up

A subject 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 subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule.
- Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject or through their family, or by contact with subject's current physician by e.g. repeat telephone calls, certified letter to the subject´s last known mailing address or local equivalent methods. If publicly death registry is available, death information (i.e. Date of death) should be collected where allowed by Regulatory and EC Requirements.
- All attempts to contact the subject should be made routinely and recorded in eCRF on the survival status module. The site should report the attempted date of contact and the last date known to be alive.
- If contact or registry/public source was unsuccessful (or no clear status could be obtained) choose subject status "unknown" and continue the contact attempts until end of the study (until final analysis).
- Patients should not be marked as lost to follow-up on the Termination (DS) module until the end of the study (at final analysis) when all attempts to collect survival follow-up have been exhausted.
- At the time of final analyses, all enrolled subjects' survival status in the safety analysis set should be re-checked, this includes those subjects who withdraw consent or are classified as "lost to follow up."
  - Lost to Follow up - site personnel should check hospital records, the subjects' current physician, and a publicly available death registry (if available) to obtain a current survival status in the 7 days following data cut-off. (The SURVIVE module will be updated.)
  - In the event that the subject has actively withdrawn consent to the processing of their personal data, the survival status of the subject can be obtained by site personnel from publicly available death registries (if available) where it is possible to do so under applicable local laws to obtain a current survival status in the 7 days following data cut-off. (The applicable CRF modules will be updated.)

7.3 Withdrawal from the study

A subject may withdraw from the study (e.g., withdraw consent), at any time (investigational product **and** assessments) at his/her own request, without prejudice to further treatment. Such subjects will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen by an investigator and undergo the assessments and procedures scheduled for the post study assessment (see Section 7.1). Adverse events should be followed up (see Sections 8.3.2 and 8.3.3) and study drug should be returned by the subject.

Subjects who withdraw consent should still be encouraged to complete the safety follow-up assessments before withdrawing consent, but these assessments cannot be mandated once consent is withdrawn. In the event that subject has actively withdrawn consent to the processing of their personal data, the survival status of the subject can be obtained by site personnel from publicly available death registries (if available) where it is possible to do so under applicable local laws to obtain a current survival status in the 7 days following data cut-off. (The applicable CRF modules will be updated.)

If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records. If samples already have been analyzed at the time of the request, AstraZeneca will not be obliged to destroy the results of this research.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA Section 1.1.

The investigator will ensure that data are recorded on the electronic Case Report Forms. The Web Based Data Capture (WBDC) system will be used for data collection and query handling.

The investigator ensures the accuracy, completeness and timeliness of the data recorded and for the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed electronic Case Report Forms. A copy of the completed electronic Case Report Forms will be archived at the study site.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue Study treatment.

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

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of

all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

Demographic data and other characteristics will be recorded and will include date of birth, age, gender, race, alcohol consumption, smoking history.

A standard medical, medication and surgical history will be obtained with review of the selection criteria with the subject. Procedures conducted as part of the subject's routine clinical management (e.g., tumor assessments, bone marrow aspirate/biopsy) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1 Efficacy assessments

8.1.1 Tumor assessments

Response assessments should not be performed while subjects are receiving systemic or enteric corticosteroids for treatment-emergent comorbid conditions.

Note: Transient worsening of disease during temporary interruption of study therapy (e.g., for drug-related toxicity, surgery, or intercurrent illness) may not indicate disease progression. In such circumstances, and if medically appropriate, subjects may resume therapy and relevant clinical, laboratory, and/or radiographic assessments should be done to document whether tumor control can be maintained or whether actual disease progression has occurred.

8.1.1.1 NHL (MCL, DLBCL, FL, SLL) tumor assessment

A pretreatment CT scan with contrast (unless contraindicated) is required for the neck, chest, abdomen, and pelvis and any other disease sites within 28 days before the first dose of study drug. Additionally, for subjects with DLBCL and MCL, a PET-CT scan will be performed within 60 days before first dose of study drug. For other diseases, a baseline PET-CT scan is not required; however, if a recent PET-CT scan (within 60 days of the first dose) is available the information should be recorded in the eCRF. Bone marrow aspirate/biopsy within 60 days before first dose of study drug is also required per clinical guidelines. Information on extranodal involvement will also be recorded. No anti-cancer treatment other than study treatment can be implemented between the earliest date of pretreatment scans or bone marrow biopsy and the initiation of study treatment.

For subjects with FL and SLL, CT scans with contrast (unless contraindicated) of the neck, chest, abdomen, and pelvis and any other disease sites will be done for tumor assessments at the end of Cycle 2 (± 7 days), Cycle 4 (± 7 days), and Cycle 6 (± 7 days); and then every 3 cycles (12 weeks ± 7 days) thereafter or more frequently at investigator discretion, until

disease progression, regardless of whether the subject receives a new anticancer therapy. Bone marrow is required for confirmation of CR per clinical guidelines.

For subjects with DLBCL and MCL, tumor assessments could include physical exam, radiographic examination, endoscopy, and bone marrow assessment. Bone marrow assessments are required for confirmation of CR for subjects who have disease involvement at screening per clinical guidelines (see Section 1.1). If GI tract involvement is suspected and supported by imaging, an endoscopy at baseline should be obtained. If GI tract involvement is suspected though not supported by imaging, an endoscopy at baseline may be obtained as clinically indicated at investigator's discretion. Endoscopy is required to confirm CR for any subjects with a documented history of GI tract involvement. During treatment, CT scans with contrast (unless contraindicated) of the neck, chest, abdomen, and pelvis and any other disease sites will be performed for tumor assessments at the end of Cycle 2 (± 7 days), Cycle 4 (± 7 days), and Cycle 6 (± 7 days); and then every 3 cycles (12 weeks ± 7 days) thereafter or more frequently at investigator discretion, until disease progression, regardless of whether the subject receives a new anticancer therapy. During treatment, PET-CT scans will be performed at the end of Cycle 2 (± 7 days) and Cycle 6 (± 7 days) and are required to confirm CR or as clinically indicated. Subjects with confirmed CR are not required to undergo further PET-CT scans on study unless there is suspicion of progressive disease in CT but cannot be proven, PET-CT may be used at the investigator's discretion.

For subjects with MCL, blinded independent central review (BICR) will be provided by a third-party vendor company, as part of endpoint assessment. The assessment results from BICR will not be reported back to the site. De-identified copies of all radiology results may be requested by the sponsor. Subjects who have signs and symptoms of progression outside of the scheduled assessment should be evaluated by the investigator with a physical exam and laboratory assessments to determine if disease progression is present. Any suspected case of disease progression should be confirmed with a CT and should be reported to the sponsor or designee. It is recommended that disease progression identified by PET-CT alone be confirmed by an alternative imaging modality (e.g., diagnostic quality CT) or by biopsy. Subjects may continue study treatment until progression is confirmed by a serial exam at least 2 weeks later. In addition, when clinically appropriate, based on investigator-perceived risk/benefit assessment, a subject may continue treatment until objective progression is confirmed. New anticancer therapy should be withheld if clinically appropriate in the absence of objectively confirmed progressive disease.

The CT portion of a PET-CT may be submitted in lieu of a dedicated CT; however, certain radiologic requirements are needed for acceptance, provided it is of diagnostic quality. Magnetic resonance imaging (MRI) may be used for subjects who are either allergic to CT contrast media or have renal insufficiency that per institutional guidelines restricts the use of CT contrast media.

All subjects should have radiographic tumor measurements performed at the participating study center or an acceptable alternate imaging facility using an identical imaging protocol and similar equipment. The same imaging equipment should be used for all scans whenever possible. The same radiologist should be assigned to read all the scans for a given subject throughout the study.

There must be radiographically measurable disease at screening (have ≥1 nodal lesion >2.0 cm in the longest diameter, and/or extranodal lesion >1.0 cm in the longest diameter as assessed by computed tomography scan). Target lesions should not be selected from previously irradiated areas. If the sole lesion lies within the field of prior radiotherapy, there must be evidence of disease progression in that lesion to be selected as target lesion. For each subject, up to 6 measurable nodal and/or extranodal lesions (i.e., per Lugano Classification, nodal lesion >1.5 cm in the longest diameter or extranodal lesions >1.0 cm in the longest diameter, clearly measurable in 2 perpendicular dimensions) will be selected as target lesions and followed up throughout the study. Measurable sites of disease should be chosen to fully represent the subject's disease in disparate anatomy or organs which are significantly involved. Any additional measurable lesions should be selected as non-target lesions. The cranial-caudal measurement of the spleen will be assessed at screening and all subsequent response evaluations. It is important to follow the assessment schedule as closely as possible. Please refer to the Schedule of Activities in Section 1.1.

In the event disease progression is suspected due to physical examination or laboratory test, a CT scan must be performed to confirm disease progression. If disease progression is suspected but indeterminate in the CT scan, a PET-CT may be used at the investigator's discretion. The investigator must evaluate the response of the subject with NHL per Lugano criteria (Cheson 2014) (Table 8)

Table 8 Response assessment criteria for NHL (Cheson 2014)

Response and Site	PET-CT-Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extra lymphatic sites	Score 1, 2, or 3[a] with or without a residual mass on 5PS[b]	Target nodes/nodal masses must regress to ≤1.5 cm in LDi

Table 8 Response assessment criteria for NHL (Cheson 2014)

Response and Site	PET-CT-Based Response	CT-Based Response
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in the marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extra lymphatic sites	Score 4 or 5[b] with reduced uptake compared with baseline and residual mass(es) of any size	≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 x 5 mm as the default value
		When no longer visible, 0 x 0 mm
	At end of treatment, these findings indicate residual disease	For a node >5 x 5 mm, but smaller than the normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
New lesions	None	None

Table 8 Response assessment criteria for NHL (Cheson 2014)

Response and Site	PET-CT-Based Response	CT-Based Response
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	<50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly

Table 8 Response assessment criteria for NHL (Cheson 2014)

Response and Site	PET-CT-Based Response	CT-Based Response
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS = 5-point scale; CT = computed tomography; FDG = [18F] fluorodeoxyglucose; IHC = immunohistochemistry; GI = gastrointestinal; LDi = longest transverse diameter of a lesion; MRI = magnetic resonance imaging; PET = positron emission tomography; PPD = cross product of the LDi and perpendicular diameter; SDi = shortest axis perpendicular to the LDi; SPD = sum of the product of the perpendicular diameters for multiple lesions.

a. A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, and lungs), GI tract involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measureable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).
b. PET 5PS: 1, no uptake above background; 2. Uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

8.1.1.2 CLL tumor assessment

Overall response assessments for CLL subjects will be based upon evaluation of physical exams, recording of symptoms, radiologic evaluations, and hematologic evaluations per the Schedule of Activities. Subjects who have signs and symptoms of disease progression outside of the scheduled study visits and assessments should be evaluated by the Investigator with a physical exam and a CBC with differential to determine if disease progression is present. The blood samples for response or disease progression determination should be confirmed by a central laboratory (not applicable for Phase 1 CLL subjects; samples from local laboratories can be used if central testing is unavailable). Any suspected case of disease progression (in the absence of laboratory or histopathologic changes meeting the criteria for PD) should be confirmed with a CT scan and should be reported to the Sponsor or designee. In addition,

when clinically appropriate, based on Investigator-perceived risk-benefit assessment, a subject may continue treatment and remain under close observation until progression is confirmed. New anticancer therapy should be withheld if clinically appropriate in the absence of confirmed progressive disease.

Baseline:

For baseline, a CT scan with contrast (MRI should be used if contraindicated) is required to cover the neck, chest, abdomen, and pelvis and any other disease sites (e.g. brain), within 28 days before the first dose of study drug. Spleen and liver size should be recorded in CT measurement. Additionally, bone marrow aspiration and biopsy within 3 months before first dose of study drug is required. Physical exam (especially lymph node and organomegaly), B symptoms, blood counts with differential and other clinical information should be recorded in the eCRF at the baseline. PET-CT is not required, but if performed within 60 days before the study treatment, should be recorded in eCRF.

There must be radiographically measurable disease at screening (have ≥1 nodal lesion >2.0 cm in the longest diameter). Up to 6 measurable disease (only nodal lesions ≥ 1.5 cm in the longest diameter, clearly measurable in 2 perpendicular dimensions, clearly measurable in 2 perpendicular dimensions), will be followed as target lesions for each subject. Measurable sites of disease should be chosen such that they are representative of the subject's disease. In addition, selection of target lesions should be from as disparate regions of the body as possible when these areas are significantly involved. Target lymph nodes should not be selected from previously irradiated areas. If the sole measurable lesion lies within the field of prior radiotherapy, there must be evidence of disease progression in that lesion that has not been previously irradiated. If additional lesions are present but are not included in the target lesion assessment, they can be added as non-target lesions followed throughout the study. The cranial-caudal measurement of the spleen and longest diameter of the liver will be assessed at screening and all subsequent response evaluations.

Follow-up:

Radiologic tumor assessment will be performed every 12 weeks (± 7 days) with the first on-treatment radiologic assessment occurring on Cycle 4 Day 1, the second on treatment scan on Cycle 7 Day 1, and so on through Cycle 25, and then every 24 weeks (± 7 days) thereafter. For subjects who achieve a response (CR, CRi, PR, or nPR), CT and overall response assessment must be performed for response confirmation in 12 weeks (±7 days) after the initial response imaging assessment, and then every 24 weeks (±7 days) thereafter. Clinical assessments should be done at every visit that physical exam and hematology test are performed.

If the subject's physical examination findings, laboratory evaluations (with hematology profile including absolute lymphocyte count, ANC, platelet count, and Hgb), and radiographic evaluations suggest that CR/CRi has been achieved in all response parameters, a bone marrow aspirate and biopsy must be obtained to confirm the CR and peripheral blood sample must be obtained to evaluate minimal residual disease (MRD) (MRD is not required for CLL subjects in Phase 1). The bone marrow aspirate and biopsy must be done between 8-12 weeks of the CT imaging that supported the assessment of CR/CRi. Subjects who are otherwise in a complete remission, but have bone marrow nodules that can be identified histologically, should be considered to have "nodular PR (nPR)." Immunohistochemistry should be performed to define whether these nodules are composed of primarily T cells, lymphocytes other than CLL cells, or CLL cells. If the nodules are not composed of CLL cells, a CR can be documented provided all other criteria are met. In cases where cytopenic progression is suspected, a bone marrow aspirate or biopsy must be performed to distinguish autoimmune and drug-related cytopenias. In cases where Richter's transformation is suspected (e.g., rapidly progressive B symptoms; bulky lymphadenopathy; organomegaly; anemia; a low platelet count; and elevated serum LDH, calcium, and β2 microglobulin levels) diagnosis should be confirmed by biopsy of lymph nodes, bone marrow, or involved organs. Pathology analyses will be done for confirmation of Richter's transformation. Biopsy of the affected site is diagnostic and sufficient for confirmation. If per local standard of care or at Investigator discretion an ancillary whole body PET-CT scan (not required for study) is performed, the results of this scan should be captured in the eCRF.

A central imaging service will be used to provide independent radiologic assessments for the purposes of the primary endpoint. Results of the review will not report back to site.

The investigator must evaluate the response of the subject per iwCLL criteria (Table 9).

Table 9 Response Assessment Criteria for CLL (modified from Hallek 2018) – iwCLL Criteria **

Group	Parameter	CR *	PR #	PD	SD
A	Lymph nodes	None ≥1.5 cm	Decrease ≥50% (from baseline)[a]	Increase ≥50% from baseline or from response	Change of -49% to +49%
	Liver and/or spleen size[b]	Spleen size <13 cm; liver size normal	Decrease ≥50% (from baseline)	Increase ≥50% from baseline or from response	Change of -49% to +49%
	Constitutional symptoms	None	Any	Any	Any

	Circulating lymphocyte count	Normal	Decrease ≥50% from baseline	Increase ≥50% over baseline	Change of -49% to +49%
B	Platelet count	≥100,000/µL	≥100,000/µL or increase ≥50% over baseline	Decrease of ≥50% from baseline secondary to CL	Change of -49% to +49%
	Hemoglobin	≥11.0 g/dL (untransfused and without erythropoietin)	≥11 g/dL or increase ≥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	Normocelluar, no CLL cells, no B-lymphoid nodules	Presence of CLL cells, or of B-lymphoid nodules, or not done	Increase of CLL cells by ≥50% on successive biopsies	No change in marrow infiltrate

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

Note: CR, complete remission: all of the criteria have to be met; PR, partial response: 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 one parameter of both groups A and B is abnormal prior to therapy, only 1 needs to improve. PD, progressive disease: at least one of the above criteria of group A or group B has to be met; SD, stable disease: all of the above criteria have to be met. Constitutional symptoms alone do not define PD.

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

b. 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.

* CRi (CR with incomplete bone marrow recovery) refers to subjects who fulfill all the criteria for a CR (including the bone marrow examinations), but have a persistent anemia, thrombocytopenia, or neutropenia apparently unrelated to CLL, but related to drug toxicity. Subjects who are otherwise in a complete remission, but bone marrow nodules can be identified histologically, should be considered to have "nodular PR (nPR)." Immunohistochemistry should be performed to define whether these nodules are composed of primarily T cells, lymphocytes other than CLL cells, or CLL cells. If the nodules are not composed of CLL cells, a CR can be documented provided all other criteria are met.

PRL (partial response with lymphocytosis): presence of lymphocytosis, plus ≥ 50% reduction in lymphadenopathy and/or in spleen or liver enlargement, plus one of the PR criteria for platelets or hemoglobin have to be met.

**patients who previously assessed based on Hallek 2008 per initial protocol should be re-evaluated based on Hallek 2018 if possible.

For a detailed description of the response parameters see Hallek 2018.

In particular, given the known mechanism of action of BCR-inhibiting agents including acalabrutinib, treatment-related lymphocytosis is an expected and frequent phenomenon observed with initiation (or re-initiation) of BTK inhibitors. 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. In such cases, increased lymphocytosis alone is not a sign of treatment failure or PD.

8.1.2 Minimal Residual Disease (CLL subjects in phase 2 – cohort B)

If the subject's physical examination findings, laboratory evaluations, and radiographic evaluations suggest that PR, CR or CRi has been achieved, a peripheral blood by flow cytometry sample to evaluate MRD should be done between 8-12 weeks from the time of supportive clinical assessments including CT imaging of suspected PR, CR or CRi.

A peripheral blood sample testing for minimal residual disease (MRD) will be done at screening and end of treatment visit or if not taken at the EoT visit, then it can be drawn at SFU visit.

Samples for the MRD tests will be sent to the central laboratory for analysis as per instructions in the laboratory manual.

8.1.3 Clinical laboratory assessments

See Table 10 for the list of clinical safety laboratory tests to be performed and to the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in the table, must be conducted in accordance with the laboratory manual and the SoA.

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables.

For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.7.

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

The clinical chemistry, hematology (see paragraphs below for specific requirements for CLL subjects in phase 2 – cohort B), pregnancy test, coagulation, urinalysis, hepatitis, HIV and serum immunoglobulin levels analyses will be performed locally at the visits as indicated in the SoA (see Table 1, Table 2 and Table 3), therefore sample volumes may vary according to local practice. If screening assessment clinical chemistry, hematology, coagulation and urinalysis are performed within 5 days prior to the baseline visit (i.e. first dose day: Phase 1 portion- at Cycle 0 Day 1; Phase 2 portion- at Cycle 1 Day 1), they do not need to be repeated at the baseline visit. T/B/NK cell count (i.e., CD3, CD4, CD8, CD19, CD16/56) will be performed at the central laboratory, samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

All samples will be used up, or disposed of after analyses.

Additional laboratory tests requirement for CLL subjects in phase 2 – cohort B only:

Hematology will be evaluated at the central laboratory and will include a complete blood count (CBC) with differential including, but not limited to white blood cell count, hemoglobin, hematocrit, platelet count, ANC, and ALC. Any missing central laboratory blood samples should be redrawn as soon as possible. In the event that the missing central laboratory sample is unrecoverable, local laboratory results will be collected, if available, and entered in the clinical database. β2-microglobulin: peripheral blood samples will be collected and sent to the central laboratory for β2-microglobulin test.

Cytogenetics and FISH Panel: screening peripheral blood (required) will be sent to a central laboratory to be tested for Del 17p, Del 13q, trisomy 12, Del 11q by FISH and stimulated karyotyping. A blood sample for FISH evaluation will also be drawn when a subject has disease progression at the EoT or SFU visits.

Genetic and molecular prognostic molecules: screening peripheral sample will be sent to central laboratory for sequencing of immunoglobulin heavy-chain variable (IGHV) and p53 mutational status. If the progression peripheral blood sample is not taken at the EoT visit, then it can be drawn at the SFU visit. Any systematic anti-cancer treatment(s) between confirmed progression and SFU visit with sample drawn should be documented.

Table 10 Laboratory variables

Clinical Chemistry [a]	
Calcium	Urea or blood urea nitrogen
Chloride	Uric acid
Magnesium	Creatinine
Phosphate/Phosphorus	Total bilirubin
Potassium	Glucose
Sodium	Albumin
AST	Total protein
ALT	Triglycerides
Alkaline phosphatase (ALP)	Cholesterol
Gamma glutamyl transferase (GGT)	Lactate dehydrogenase (LDH)
Haematology [b]	
White blood cell (WBC) count with differential	Platelet count
Red blood cell (RBC) count	Absolute neutrophil count (ANC)
Haematocrit	Absolute lymphocyte count (ALC)

Haemoglobin	
Urinalysis	
pH	Bilirubin
Specific gravity	Protein
Glucose	Ketones
Blood	
Pregnancy Test (females of childbearing potential only)	
Urine human chorionic gonadotropin (hCG) or Serum βhCG	
Hepatitis B and C Testing [c]	
HBsAg	Hepatitis B surface antibody (HBsAb)
Anti-HBc	Hepatitis C (hepatitis C virus [HCV]) antibody
Hepatitis B PCR (clinically indicated)	Hepatitis C PCR (clinically indicated)
Coagulation	
Coagulation tests: prothrombin time (PT)	Activated partial thromboplastin time (aPTT)
Fibrinogen	
Other Tests	
T/B/NK Cell Count	Serum immunoglobulin levels
HIV antibody	β2-microglobulin [d]
Cytogenetics and FISH Panel [d,e]	Genetic and molecular prognostic molecules[d,f]

a. In case a subject shows an AST or ALT ≥3xULN together with total bilirubin ≥2xULN please refer to Appendix D. 'Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law', for further instructions.
b. Hematology will be evaluated at the central laboratory for CLL subjects in phase 2 – cohort B.
c. Hepatitis serology testing must include HBsAg, HBsAb, anti-HBc and hepatitis C (HCV) antibody. In addition, any subjects testing positive for anti-HBc must have quantitative PCR testing for HBV DNA during screening and monthly basis from Cycle 2 through 19. After Cycle 19, monitoring will occur every 3 months. HBV monitor should continue until 12 months after last dose of study drug (see Table 1, Table 2, Table 3 and exclusion criterion #7). Any subject with a rising viral load (above lower limit of detection) should discontinue study drug and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B. Since IVIG may cause false positive hepatitis serology, monthly PCR testing is not required in subjects who are currently receiving or received prophylactic IVIG within 3 months 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 (e.g., in the setting of rising transaminase levels). Refer to Table 1 , Table 2 and Table 3 regarding monitoring of subjects who are anti-HBc positive or who have a known history of HBV.
Subjects with a known history of hepatitis C or who are hepatitis C antibody positive should have quantitative PCR testing for HCV RNA performed during screening. No further testing is necessary if the PCR results are negative at screening.

d. These tests will be performed at the central laboratory and for CLL subjects in cohort B only.
e. Cytogenetics and FISH Panel include Del 17p, Del 13q, trisomy 12, Del 11q by FISH and stimulated karyotyping.
f. Genetic and molecular prognostic molecules panel include, but is not limited to, sequencing of p53 mutations, immunoglobulin heavy-chain variable (IGHV) mutational status.

8.1.4 B-Symptoms

B-symptoms are constitutional symptoms defined as any one or more of the following disease-related symptoms or signs:

- Unintentional weight loss of 10% or more within the previous 6 months
- Significant fatigue (i.e., ECOG performance status 2 or worse; inability to work or perform usual activities)
- Fevers >100.5°F or 38.0°C for ≥2 weeks without other evidence of infection
- Night sweats for >1 month without evidence of infection

B-symptoms is part of tumor response assessment for CLL subjects per Hallek 2018.

B-symptoms should not be reported as AEs. Worsening is generally considered a symptom (but not an objective criterion) of progression.

8.2 Safety assessments

Standard collection of AE data and other study variables (eg. vital signs, 12 lead ECG, blood sampling for haematology, clinical chemistry and coagulation, urinalysis etc.) will be carried out according to the Schedule of Activities.

8.2.1 Clinical safety laboratory assessments

Clinical safety laboratory assessment is included in Table 10 and specified into the SoA for the timing and frequency.

8.2.2 Physical examinations

The physical examination includes 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 nervous system examination will include attention to neurologic signs and symptoms of PML. The lymphatic system examination will include bidimensional measurements of palpable lymph nodes. Enlargement of the spleen and liver will be assessed by measuring the costal margin and past-medioclavicular line, respectively. Only a qualified healthcare provider should perform the lymphatic system examination. As much as possible, the same person should perform all the lymphatic exams for a given subject.

Changes from baseline abnormalities should be recorded in subject notes. New or worsened clinically significant abnormalities should be recorded as AEs on the Adverse Event eCRF.

Physical examination will be performed at timelines as specified in the SoA. Investigators should pay special attention to clinical signs related to previous serious illnesses, new or worsening abnormalities may qualify as adverse events, see Section 8.3.7 for details.

8.2.3 Vital signs

Vital signs (Blood pressure, pulse rate, and body temperature) should be assessed after at least 5 minutes of rest for the subject in a quiet setting without distractions (e.g., television, cell phones).

Changes from baseline abnormalities should be recorded in subject notes. New or worsened clinically significant abnormalities should be recorded as AEs on the Adverse Event eCRF.

8.2.4 Electrocardiograms

Twelve-lead ECG will be obtained as outlined in the SoA (see Section 1.1) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Study -related ECG should be done after the subject has been resting supine for at least 10 minutes. A standardized ECG machine should be used and the subject should be examined using the same machine throughout the study if possible.

On the intensive PK sampling days (Cycle 0 Day 1 and Cycle 1 Day 8), the assessment will be performed at 1-2 hours post (morning) dose. The timing and number of ECGs may be altered depending on the emerging PK and safety profile.

After paper ECGs have been recorded, the investigator or designated physician will review each of the ECGs and may refer to a local cardiologist if appropriate. A paper copy should be filed in the patient's medical records.

If an abnormal ECG finding at screening or baseline is considered to be clinically significant by the investigator, it should be reported as a concurrent condition. For all ECGs details of rhythm, ECG intervals and an overall evaluation will be recorded.

8.2.5 ECOG performance status

ECOG performance status will be assessed at screening, prior to the first dose of study treatment and at all visits thereafter according to ECOG criteria as follows: It is recommended, where possible, that a subject's performance status be assessed by the same person throughout the study.

Grade	ECOG

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, e.g., light house work, 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

8.3 Collection of adverse events

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

The definitions of an AE or SAE can be found in Appendix B.

AE will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow/up AEs see Section 8.3.3.

8.3.1 Method of detecting AEs and SAEs

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

8.3.2 Time period and frequency for collecting AE and SAE information

AEs and SAEs will be collected from time of signature of informed consent form until 30 days after the last dose of study treatment or the start of new anticancer therapy (whichever comes first). After this period, investigators should report SAEs or other AEs of concern that are believed to be related to prior treatment with study treatment.

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

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

All SAEs/AESIs will be recorded and reported to the sponsor or designee within 24 hours. The investigator will submit any updated SAE/AESI data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject's last visit and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator may notify the sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix B.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAE/non-serious AEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up.

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

8.3.4 Adverse event data collection

The following variables will be collected for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- CTCAE grade (version 5.0)/changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product(s) (Yes or No)
- Action taken with regard to Investigational Product(s)
- Whether the AE caused subject's withdrawal from study (Yes or No)
- Outcome
- Administration of treatment for the AE

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

- Date AE met criteria for serious AE

- Date investigator became aware of serious AE
- AE is serious due to
- 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
- Description of the SAE

8.3.5 Causality collection

The Investigator will assess causal relationship between Investigational Medicinal Product and each AE and/or incident, 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 IMP?'

For SAEs and serious incident, causal relationship should 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 B7 to the Clinical Study Protocol.

8.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or care provider or reported in response to the open question from the study site staff: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.7 Adverse events based on examinations and tests

The results from the Clinical Study Protocol mandated laboratory tests, vital signs, ECGs and other safety assessment will be summarized in the CSR. Deterioration as compared to baseline in these parameters will therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value, vital sign, ECG or other safety assessment is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (e.g., anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated 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 progression.

8.3.8 Adverse events of special interest

Adverse events of special interest (AESIs) are events of scientific and medical interest specific to the further understanding of the acalabrutinib safety profile and require close monitoring and rapid communication by the investigators to the sponsor. An AESI can be serious or non-serious.
All AESIs will be recorded and reported to the sponsor or designee within 24 hours. The investigator will submit any updated AESI data to the sponsor within 24 hours of it being available. Serious AESIs will be recorded and reported as per Section 8.4.1.

The following events are AESIs for subjects who receive acalabrutinib and must be reported to the sponsor expeditiously irrespective of regulatory seriousness criteria or causality:
• Ventricular arrhythmias (e.g., ventricular extrasystoles, ventricular tachycardia, ventricular arrhythmia, ventricular fibrillation, etc.)

8.3.9 Hy's law

Cases where a subject shows elevation in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3xULN together with total bilirubin ≥ 2xULN may need to be reported as SAEs. Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

8.3.10 Disease progression

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or aggravation in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. **Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.**

8.3.11 New cancers

The development of a new cancer should be regarded as an AE and will generally meet at least one of the serious criteria. New primary cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the patient's inclusion in this study. They do not include metastases of the original cancer.

8.3.12 Handling of deaths

All deaths that occur during the study, or within the protocol-defined follow-up period after the administration of the last dose of investigational product, should be reported as follows:

- Death, which is unequivocally due to disease progression, should be communicated to the study monitor at the next monitoring visit and should be documented in the eCRF module, but should not be reported as a SAE during the study
- Where death is not due (or not clearly due) to disease progression of the disease under study, the AE causing the death should be reported to the study monitor as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign a single primary cause of death together with any contributory causes
- Deaths with an unknown cause should always be reported as a SAE but every effort should be made to establish a cause of death. A post-mortem may be helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results (with translation of important parts into English) should be reported in an expedited fashion to an AstraZeneca representative within the usual timeframes.

Deaths occurring after the protocol-defined reporting period (30 days after the last dose of study treatment) should be documented in the Death page. If the death occurred as a result of an event that started after the defined follow-up period and the event is considered to be due to a late-onset toxicity to study treatment, then it should also be reported as an SAE.

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works 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 adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the Investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

For further guidance on the definition of a SAE, see Appendix B of the Clinical Study Protocol.

8.4.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for: If the pregnancy is discovered before the study subject has received any study drug.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4.2.1 Maternal exposure

If a subject becomes pregnant during the course of the study, investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies /birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs during exposure to investigational product and until 2 days after the last dose of acalabrutinib, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 8.4.1) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

8.4.2.2 Paternal exposure

Pregnancy of the participant's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose of study intervention until 2 days after the last dose of acalabrutinib, should be followed up and documented in the medical record and provided to the sponsor Patient Safety data entry site. Consent from the partner must be obtained before the information is collected and reported to AstraZeneca.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the investigator must obtain the consent of the participant's partner. The local study team should adopt the Master Pregnant Partner Form in line with local procedures/requirements and submit it to the relevant Regulatory Authority/IRBs/IECs prior to use.

8.4.3 Overdose

For this study, any dose of acalabrutinib greater than the dose being studied will be considered an overdose. However, if acalabrutinib is administered with strong CYP3A inducers, the recommended dose is 200mg BID (Table 6). It is not considered as overdose in this situation. Avoid co-administration of strong CYP3A inducers with acalabrutinib.

For any subject experiencing an acalabrutinib overdose, observation for any symptomatic side effects should be instituted, and vital signs, biochemical and hematologic parameters, and ECGs 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.

Such overdoses should be recorded as follows:

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module

If an overdose on an IMP/study intervention occurs in the course of the study, then the investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **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 provided to the AstraZeneca Patient Safety data entry site within one or 5 calendar days for overdoses associated with a SAE (see Section 8.3.2), and within 30 days for other overdoses

8.4.4 Medication Error, Drug Abuse, and Drug Misuse

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 i.e., 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 events) **or 5** (other serious initial and follow up events) **calendar days** if there is an SAE associated with the event of medication error, drug abuse, or misuse (see Section 8.3.2) and **within 30 days** for all other medication errors.

8.4.4.1 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 Non Investigational Medicinal Product 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 B 8.

8.4.4.2 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 B 8.

8.4.4.3 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 authorised product information, or

for unauthorised 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 B 8.

8.4.5 Management of IP-related toxicities Dose Modification

Dose Modification Management of IP-related toxicities can be found in Section 6.6.

8.5 Pharmacokinetics

8.5.1 Collection of pharmacokinetic samples

In Phase 1 portion, venous blood samples for determination of concentrations of acalabrutinib and its metabolite (ACP-5862) in plasma will be taken at the times presented in Table 11 and Table 12. The date and time of collection of each sample will be recorded.

The timing of the pharmacokinetic samples may be adjusted during the study, dependent on emerging data, in order to ensure appropriate characterization of the plasma concentration-time profiles.

Table 11 Pharmacokinetic sampling schedule (Single dose, Phase 1 portion)

Cycle	Day	Pre-dose***	Hours Post-dose										
			0.25 (±1min)	0.5 (±5min)	0.75 (±5min)	1*	2*	4*	6*	8*	12*	24*	48*
0	1	X	X	X	X	X	X	X	X	X	X	X	X**

* Time allowance: ±10 min
** Before Cycle 1 Day 1 morning dose
*** Within 10 min prior to dosing

Table 12 Pharmacokinetic sampling schedule (Multiple doses, Phase 1 portion)

Cycle	Day	Pre-dose***	Hours Post-dose								
			0.25 **(±1 min)**	0.5 **(±5 min)**	0.75 **(±5 min)**	1*	2*	4*	6*	8*	12*
1	8	X	X	X	X	X	X	X	X	X	X**
1	28					X (±0.5 hr)	X (±0.5 hr)	X (±1 hr)			

* Time allowance: ±10 min
** Before Cycle 1 Day 8 evening dose
*** Within 10 min prior to dosing

In Phase 2 portion, the schedule of sparse PK sampling for determination of acalabrutinib plasma concentration is presented in Table 13.

Table 13 Sparse pharmacokinetic sampling schedule in Phase 2 portion

Cycle	Day	Hours Post-dose		
		1 (± 0.5 hr)	2 (± 0.5 hr)	4 (± 1 hr)
1	8	X	X	X
1	15 or 22	X	X	X

All timepoints are relative to the morning dose.

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

8.5.2 Determination of drug concentration

Samples for determination of acalabrutinib concentration in plasma will be analyzed by analytical test sites on behalf of AstraZeneca, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

8.5.3 Storage and destruction of pharmacokinetic samples

Pharmacokinetic (PK) samples will be disposed of 6 months within final Bioanalytical Report publication.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a Bioanalytical Report.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

Genetic testing is not evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Health Economics

Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

Refer to Section 9.2 for details.

9.2 Sample size determination

The primary objectives of Phase 1 portion are to evaluate the safety, tolerability and pharmacokinetics (PK) of acalabrutinib. Hence approximately 12 subjects will be enrolled in Phase 1 to obtain adequate pharmacokinetic and safety data. Additional subjects may be enrolled to ensure at least 8 eligible subjects for evaluable single- and multiple-dose PK profiles based on China regulatory considerations.

For Phase 2 of the study, approximately 33 R/R MCL subjects (Cohort A) and 60 R/R CLL subjects (Cohort B) will be enrolled in order to evaluate the efficacy in R/R MCL and R/R CLL subjects. For Cohort A, a sample size of 33 subjects will provide a 95% two-sided confidence interval centered around an expected ORR of 80% that excludes an ORR of 60% as a lower bound. With 60 subjects from Cohort B, an exact binomial test with a nominal one-sided 2.5% significance level will have 90% power to detect the difference between a null hypothesis ORR of 70% and an alternative ORR of 88%.

9.3 Populations for analyses

For purposes of analysis, the following populations are defined:

Analysis set	Description
Safety analysis set	All subjects who received at least 1 dose of acalabrutinib.
Pharmacokinetics analysis set	Dosed subjects with reportable acalabrutinib plasma concentration and PK parameter data with no important protocol deviations that may impact PK.
Tumor response analysis set	Dosed subjects with a relevant baseline tumor assessment.

9.4 Statistical analyses

Analyses will be performed by AstraZeneca or its representatives. A comprehensive statistical analysis plan will be developed and finalized before database lock. 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 clinical study report.

There are two planned analyses for all subjects of Phase 1 portion and cohort A of Phase 2 portion.

The data cut-off for the 1st analysis will take place when both of the following two conditions are met

- Approximately 1 month after Cycle 1 day 1 of the last subject in Phase 1 to allow required PK samplings at cycle 0 and cycle 1 are collected.
- Approximately 6 months after last R/R MCL subjects across both Phase 1 and Phase 2 to allow a minimum of two tumor assessments after first dose.

A Clinical Study Report will be prepared to summarize PK, safety and efficacy data for Phase 1 portion and/or cohort A of Phase 2 portion. R/R MCL subjects in Phase 1, if applicable, will be combined together with the subjects in cohort A of Phase 2 portion for MCL analysis.

The data cut-off for the 2nd analysis will take place approximately 14 months after last subject enrolled in both Phase 1 and cohort A of Phase 2. A Clinical Study Report Addendum including all subjects of Phase 1 portion and/or cohort A of Phase 2 portion will be prepared at that time.

There are three planned analyses for R/R CLL subjects of cohort B of Phase 2 portion.

The data cut-off for the 1st analysis will take place when approximately 6 months after last R/R CLL subjects enrolled in across Phase 2. A Clinical Study Report will be prepared to summarize efficacy, safety and PK data for cohort B of Phase 2 portion. Efficacy analysis of tumor response in R/R CLL will only be applied for R/R CLL subjects in Phase 2. Tumor response of R/R CLL subjects in Phase 1 may be listed separately in a proper way.

The data cut-off for the 2nd analysis will take place approximately 12 months after last R/R CLL subject enrolled in Phase 2. A Clinical Study Report Addendum including R/R CLL subjects of cohort B of Phase 2 portion will be prepared at that time.

The data cut-off for the 3rd analysis will take place approximately 24 months after last R/R CLL subject enrolled in Phase 2. A Clinical Study Report Addendum including R/R CLL subjects of cohort B of Phase 2 portion will be prepared at that time.

Data from Phase 1 and Phase 2 will be presented separately unless specified otherwise. Regarding tumor response assessment, data from Phase 1 and Phase 2 will be combined for analysis of R/R MCL subjects. Whereas, efficacy analysis of tumor response in R/R CLL will only be applied for R/R CLL subjects in Phase 2. Selected safety summaries might be generated for R/R MCL or R/R CLL subjects across Phase 1 and Phase 2.

In general, baseline is defined as last assessment before first dose of study treatment. Demographic data, exposure and safety data will be analyzed based on safety analysis set. Pharmacokinetics will be analyzed based on PK analysis set. Efficacy analyses will be conducted on tumor response analysis set.

9.4.1 Outcome measures for analyses

9.4.1.1 Calculation or derivation of safety variables

Safety and tolerability will be assessed in terms of AEs, laboratory data, vital signs, ECG. These will be collected for all subjects. Appropriate summaries of these data will be presented as described in Section 9.4.2.

Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to discontinuation of investigational product. Based on the expert's judgement, adverse events of particular clinical importance may, after consultation with the Global Safety Physician, be considered other significant adverse events (OAEs) and reported as such in the Clinical Study Report. A similar review of laboratory values, vital signs, ECGs and other safety assessments will be performed for identification of other significant adverse events.

9.4.1.2 Calculation or derivation of pharmacokinetic variables

Pharmacokinetic analysis of the plasma concentration data for acalabrutinib and a metabolite (ACP-5862) will be performed by AstraZeneca or a Contract Research Organization on behalf of AstraZeneca. The actual sampling times will be used in the parameter calculations and PK parameters will be derived using standard non-compartmental methods.

Where possible, the following PK parameters will be determined with plasma concentration data of acalabrutinib and a metabolite (ACP-5862) on Cycle 0 Days 1 and Cycle 1 Day 8:

Maximum observed plasma drug concentration (C_{max}), time to reach maximum observed concentration (t_{max}), terminal elimination rate constant (λ_Z), half-life associated with terminal slope of a semi-logarithmic concentration-time curve ($t_{½\lambda Z}$), area under the plasma concentration-time curve from zero to 12 hours (AUC_{0-12}), from zero to the time of the last quantifiable concentration (AUClast) and from zero to infinity (AUCinf), apparent total body clearance of drug from plasma (CL/F), apparent volume of distribution (V_Z/F), accumulation ratios (R_{ac}) for AUC and Cmax, temporal change parameter (TCP), and Metabolite: Parent ratio.

The Cmax and tmax will be determined by inspection of the concentration-time profiles. Where possible the λz will be calculated by log-linear regression of the terminal portion of the concentration-time profiles where there are sufficient data, and the $t_{½\lambda z}$ will be calculated as ln2/λz. The AUC0-12, and AUClast will be calculated using the linear/log trapezoidal rule (i.e. "linear-up-log-down": the linear trapezoidal rule is used any time that the concentration data is increasing, and the logarithmic trapezoidal rule is used any time that the concentration data is decreasing). Where appropriate, the AUClast will be extrapolated to infinity using λz to

obtain AUCinf. The CL/F will be determined from the ratio of dose/AUCinf. The Vz/F will be determined from the ratio of CL/F/λz. The Rac AUC and Rac Cmax will be calculated as the ratio of the AUCτ or Cmax on Cycle 1 Day 8 and Cycle 0 Day 1, respectively. The TCP will be assessed by the calculation of the ratio of AUCτ on Cycle 1 Day 8 and AUCinf on Cycle 0 Day 1. The Metabolite: Parent ratio parameters will be calculated after molar conversion.

9.4.1.3 Calculation or derivation of efficacy variables

Overall response rate (ORR)

As for R/R MCL subjects, ORR will be defined as the proportion of subjects who achieve either a PR or CR as best overall response, according to the Lugano Classification for NHL (Cheson 2014), as assessed by BICR.

As for R/R CLL subjects, ORR will be defined as the proportion of subjects who achieve a nPR, PR, CR or CRi as best overall response, according to response assessment criteria for CLL (modified from Hallek 2018)-iwCLL Criteria, as assessed by BICR. CRi refers to patients who fulfil all the criteria for a CR (including the bone marrow examinations), but have a persistent anemia, thrombocytopenia, or neutropenia apparently unrelated to CLL, but related to drug toxicity. nPR refers to patients who fulfil all the criteria for a CR but with the presence of B-lymphoid nodules in the bone marrow which reflect residual disease.

Best overall response (BOR) is the best response a patient has had following first dose date, but prior to starting any subsequent anticancer therapy up to and including progression or the last evaluable assessment in the absence of progression, assessed by BICR.

ORR plus patients with a best overall response of PRL will also be assessed, denoted as ORR+PRL.

Duration of Response (DoR)

DoR is defined as the interval from the first documentation of objective response mentioned above to the earlier of the first documentation of objective disease progression by the BICR or death from any cause. Subjects who withdraw from the study or are considered lost to follow-up without prior documentation of disease progression will be censored on the date of the last adequate disease assessment. Subjects who start new anticancer therapy before documentation of disease progression will be censored on the date of the last adequate disease assessment that is on or before the start date of the new anticancer therapy.

Progression- free survival (PFS)

PFS is defined as the interval from the start of acalabrutinib therapy to the earlier of the first documentation of objective disease progression by the BICR or death from any cause. Subjects who withdraw from the study or are considered lost to follow-up without prior

documentation of disease progression will be censored on the date of the last adequate disease assessment. Subjects who start new anticancer therapy before documentation of disease progression will be censored on the date of the last adequate disease assessment that is on or before the start date of the new anticancer therapy. As for the detailed censoring rules, please refer to SAP.

Time to response (TTR)

TTR will be analyzed for subjects with objective response (PR or better) and is defined as the interval between the date of first dose and the date of initial documentation of a response. Time to initial response as well as time to best response will be derived.

Investigator-assessed endpoints (ORR, DoR, PFS and TTR)

ORR, DoR, PFS and TTR assessed by the investigators will be derived in the same way as BICR assessed endpoints.

Time to Next Treatment (TTNT, for R/R CLL only)

TTNT is defined as the interval from the start of acalabrutinib therapy to institution of non-protocol specified treatment for CLL or death due to any cause, whichever comes first. As for the detailed censoring rules, please refer to SAP.

Overall survival

OS is defined as the interval from the start of acalabrutinib therapy to death from any cause. Subjects who are known to be alive as of their last known status will be censored at their last date known to be alive.

Minimum Residual Disease Rate (for R/R CLL only)

Minimal residual disease negative rate is defined as the proportion of subjects with MRD-negativity measured in the peripheral blood by flow cytometry (defined as <1 CLL cell per 10,000 leukocytes).

9.4.2 Safety analyses

The Medical Dictionary for Regulatory Activities will be used to code all AEs to a system organ class and a preferred term. The severity of the AE will be assessed by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Study drug-related AEs are those assessed by investigator as related.

Treatment-emergent AEs will be summarized by system organ class and preferred terms in descending order of frequency, by CTCAE toxicity grade. Drug-related treatment-emergent AEs, serious treatment-emergent AEs and drug-related serious treatment-emergent AEs,

treatment-emergent AEs leading to treatment discontinuation, dose delay and dose modification will be summarized by preferred teams in descending order of frequency and by CTCAE toxicity grade.

All AEs will be listed. Details of any deaths will be listed for all subjects.

Hematology, clinical chemistry, vital signs, ECG data, T/B/NK Cell Count, and Serum Immunoglobulin will be listed individually by subject and suitably summarized. For all laboratory variables, which are included in the version 5.0 of CTCAE, the CTCAE grade will be calculated. Summary statistics of mean, median, standard deviation, minimum, maximum and number of observations will be used.

Graphical presentations of safety data may be presented as is deemed appropriate. This may include, but is not restricted to, presentation of parameters against time, concentration or shift plots. Appropriate scatter plots may also be considered to investigate trends in parameters compared to baseline.

9.4.3 Pharmacokinetics analyses

For Phase 1 portion, plasma concentrations of acalabrutinib and a metabolite (ACP-5862) will be summarized by nominal sample time. Plasma concentrations and derived PK parameters will be summarized. Parameters following single and multiple dosing will be summarized separately. Plasma concentrations at each time point will be summarized by the following summary statistics:

- The geometric mean (gmean, calculated as exp [μ], where μ is the mean of the data on a logarithmic scale)
- Coefficient of variation (CV, calculated as $100\sqrt{\exp(s^2) - 1}$, where s is the standard deviation of the data on a log scale)
- Gmean ± standard deviation (calculated as exp[μ±s])
- Arithmetic mean calculated using untransformed data
- Standard Deviation calculated using untransformed data
- Minimum
- Median
- Maximum
- Number of observations

The following summary statistics will be presented for all the PK parameters (except tmax) listed in Table 4:

- The geometric mean (gmean, calculated as exp [μ], where μ is the mean of the data on a logarithmic scale)

- Geometric standard deviation (GSD)
- Coefficient of variation (CV, calculated as 100 $\sqrt{\exp(s^2) - 1}$, where s is the standard deviation of the data on a log scale)
- Arithmetic mean calculated using untransformed data
- Standard Deviation calculated using untransformed data
- Minimum
- Median
- Maximum
- Number of observations

The following summary statistics will be presented for tmax:

- Median
- Minimum
- Maximum
- Number of observations

The pharmacokinetic data for acalabrutinib and a metabolite (ACP-5862) after a single-dose and a multiple-dose, respectively, will also be displayed graphically. Displays will include plasma concentration patient profiles (on the linear and log-scale) versus time and gmean concentration (on the linear and log-scale) versus time.

Scatter plots of PK parameters will be considered as appropriate.

For Phase 2 portion, plasma concentrations of acalabrutinib will be summarized and listed.

9.4.4 Efficacy analyses

For Phase 1 part, tumor response data for each subject by each visit and best overall response will be listed only. In addition, number of subject except R/R CLL patients with tumor response (CR, PR, SD, PD) will be counted and illustrated in a proper way. For R/R CLL patients, number of subject with tumor response (CR, CRi, nPR, PR, PRL, SD, PD) will be presented in a similar way.

Data from Phase 1 and Phase 2 will be combined for analysis of R/R MCL subjects. Whereas, R/R CLL efficacy analysis of tumor response will only be applied for R/R CLL subjects in Phase 2. The efficacy analysis of R/R MCL and CLL subjects will be conducted and summarized separately.

Primary analysis of BICR-assessed ORR will be conducted on the tumor response analysis set. ORR and the corresponding 95% two-sided CI of ORR will be presented based on

Clopper-Pearson exact method. Descriptive statistics will be provided for best overall response (BOR).

The analysis of BICR-assessed DoR, PFS and OS will be estimated using the Kaplan-Meier (KM) methods. KM estimates will be calculated for event time quartiles (including median), and event-free rates will be calculated at selected time points. In addition, the reason for censoring will be summarized for DoR, PFS and OS. Time to initial response (TTR) and time to best response will be summarized separately. Time to next treatment (for R/R CLL only) will be summarized using descriptive statistics.

The same analysis methods for BICR-assessed endpoints (ORR, DoR, PFS, and TTR) will be applied to investigator-assessed endpoints. The discordant responses assessed by the BICR and the investigator will be provided.

MRD negativity rate will be summarized for R/R CLL subjects only. Efficacy data of R/R CLL subjects with Del 17p will be summarized separately as appropriate. Subgroup analysis of other chromosomal abnormalities (Del 11q, IGHV mutational status, p53 mutational status, etc) will also be performed if data allows. Details will be specified at SAP.

9.5 Interim analyses

There is no interim analysis for futility or superiority planned for this study. There will be five planned DCOs, for details, please refer Section 9.4.

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11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, ethical and study oversight considerations

A 1 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 Helsinkias amended at 64th WMA General Assembly, Fortaleza, Brazil, October 2013 and CIOMS International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., 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 amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- AstraZeneca will be responsible for obtaining the required authorisations 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 (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to AstraZeneca of a SAE is essential so that legal obligations and ethical responsibilities towards 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, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from AstraZeneca will review and then file it along with the [Investigator's Brochure or state other documents] 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, investigator 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 European Medicines Agency (EMA) Clinical Trial Information System (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.

A 2 Financial disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed consent process

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

Subjects must be informed that their participation is voluntary. Subjects 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, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.

The medical record must include a statement that written informed consent was obtained before the subject 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.

Subjects must be re-consented 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 subject or the subject's legally authorized representative.

Subjects who are rescreened are required to sign a new ICF, see Section 5.4

Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. If a subject withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples already have been analyzed at the time of the request, AstraZeneca will not be obliged to destroy the results of this research.

A 4 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 which 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.

A 5 Committees structure

The safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by Safety Review Committee (SRC). Issues identified will be addressed; for instance, this could involve amendments to the Clinical Study Protocol and letters to Investigators.

Safety Review Committee

During the study, a Safety Review Committee (SRC) will evaluate the safety and tolerability of acalabrutinib.

The SRC will consist of:

- Study Physician, who will chair the committee, or delegate
- Principal Investigator or delegate from each investigational site

In addition, one other physician from the following may be invited:

- Global Safety Physician or delegate or equivalent
- Global Clinical Lead or delegate or equivalent
- Senior physician from another project

The Study Pharmacokineticist, Study Statistician, Patient Safety Scientist or equivalent, Study Delivery Leader may also be invited as appropriate. The SRC Remit document for this study will define the exact membership and who should be present for decisions to be made.

Further internal or external experts may be consulted by the SRC as necessary. The Study Safety Physician or delegate should always be present at the SRC if there are safety issues for discussion.

A 6 Dissemination of clinical study data

A description of this clinical trial will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the main study results when they are available. The clinical trial 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.

A 7 Data quality assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects 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 15 years after study completion unless local regulations or institutional policies require a longer 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.

A 8 Source documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the CRF 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.

Definitions of what constitutes source data can be found in Clinical Study Agreement.

A 9 Study and Site Closure

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 treatment development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(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.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

A 10 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 multicentre 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 B Adverse event definitions and additional safety information

B 1 Definition of adverse events

An adverse event is the development of any untoward medical occurrence (other than progression of the malignancy under evaluation) in a subject or clinical study subject 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 (e.g. 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 treatment has been administered.

B 2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

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

B 3 Life threatening

'Life-threatening' means that the subject 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 subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

B 4 Hospitalization

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

B 5 Important medical event or medical treatment

Medical and scientific judgement 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 subject or may require medical treatment 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 judgement must be used.

Examples of important medical events:

- 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 (e.g., neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

B 6 Intensity rating scale

The grading scales found in the revised National Cancer Institute CTCAE version 5.0 will be utilized 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 (http://ctep.cancer.gov).

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B2. 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 Appendix B2. 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 Appendix B2.

B 7 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 drug.

- Time Course. Exposure to suspect drug. Has the subject 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 aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca 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 no available facts or arguments to suggest a causal relationship, 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.

B 8 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 AstraZeneca study drug 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 recognize that could have led to an error

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

- Drug name confusion
- Dispensing error e.g. medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated e.g. tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g. kept in the refrigeratorwhen 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 lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) e.g. 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 purpose 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 Data Entry Site (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 authorised product information, or for unauthorised 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 C Handling of Human Biological Samples

C 1 Chain of custody of biological samples

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 subjects while in storage at the center until shipment or disposal (where appropriate).

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 documentation of receipt of arrival.

AstraZeneca 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

C 2 Withdrawal of Informed Consent for donated biological samples

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

The Investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the subject and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organizations holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (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 pathogensare e.g., 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 e.g., 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 trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial 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**
- IATA 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 D Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law

D 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report potential Hy's Law (PHL) cases and Hy's Law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a subject meets 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 alanine aminotransferase (ALT) from a central laboratory **and/or** elevated total bilirubin (TBL) from a local laboratory.

The investigator will also review adverse event (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 drug induced liver injury (DILI) caused by the investigational medicinal product (IP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting AE and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

D 2 Definitions

Potential Hy's Law (PHL)

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3× upper limit of normal (ULN) **together with** total bilirubin (TBL) ≥ 2×ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2 ×ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

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

D 3 Identification of potential Hy's Law cases

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

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

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

- Immediately notify the AstraZeneca representative.
- Determine whether the participant meets PHL criteria (see Section D 2 Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits.
- Promptly enter the laboratory data into the laboratory eCRF.

D 4 Follow-up

D 4.1 Potential Hy's Law criteria not met

If the subject does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the subject has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

D 4.2 Potential Hy's Law criteria met

If the subject does meet PHL criteria the Investigator will:

- 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 subjects that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change [#] in the subject's condition
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up and the continuous review of data.
- Subsequent to this contact the Investigator will:
  - Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician.
  - Complete the three Liver CRF Modules as information becomes available

[#] **A 'significant' change** in the subject'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.

D 5 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 was initially detected, the study physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was 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 a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF.
- If the alternative explanation is an AE/SAE, update the previously submitted PHL SAE and AE CRFs 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 IMP:

- Report updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As 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 IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the previously submitted PHL SAE report following 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.

D 6 Actions required when potential Hy's Law criteria are met before and after starting study treatment

This section is applicable to subjects with liver metastases who meet PHL criteria on Study treatment having previously met PHL criteria at a study visit prior to starting Study treatment.

At the first on-study treatment occurrence of PHL criteria being met, the Investigator will determine if there has been a **significant change** in the subjects' 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 described in Section D 4.2.

D 7 Actions required for repeat episodes of potential Hy's Law

This section is applicable when a subject meets PHL criteria on study treatment, and has already met PHL criteria at a previous on study treatment 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 criteria being met 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 (e.g., chronic or progressing malignant disease, severe infection or liver disease)?,

If **No**: Follow the process described in Appendix D 4.2for reporting PHL as an SAE

If **Yes**: Determine if there has been a significant[#] change in the subject's condition compared with when PHL criteria were previously met.

- If there is no significant change, no action is required.
- If there is a significant change# follow the process described in Appendix D 4.2 for reporting PHL as an SAE

[#]A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) 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.

D 8 Laboratory tests

Table 14 below represents a comprehensive list of follow-up tests that may aid in assessing PHL/HL. The list may be modified based on clinical judgement.

Test results used to assess PHL/HL should be recorded on the appropriate eCRF.

Table 14 Follow- up Tests for Assessing Potential Hy's Law / Hy's Law

Additional standard chemistry and coagulation tests	GGT
	LDH
	Prothrombin time
	INR
Viral hepatitis	IgM anti-HAV
	IgM and IgG anti-HBc
	HBsAg
	HBV DNA
	IgG anti-HCV
	HCV RNA [a]
	IgM anti-HEV
	HEV RNA
Other viral infections	IgM & IgG anti-CMV
	IgM & IgG anti-HSV
	IgM & IgG anti-EBV

Alcoholic hepatitis	Carbohydrate-deficient transferrin (CD-transferrin) [b]
Autoimmune hepatitis	Antinuclear antibody (ANA)
	Anti-liver/kidney microsomal Ab (Anti-LKM)
	Anti-smooth muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin
	Ceruloplasmin
	Iron
	Ferritin
	Transferrin
	Transferrin saturation
[a] HCV RNA is only tested when IgG anti-HCV is positive or inconclusive.	
[b] If carbohydrate-deficient transferrin (CD-transferrin) is not available, this list should be amended accordingly.	

References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation': https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm174090.pdf

Appendix E Known strong in vivo inhibitors or inducers of CYP3A

Strong Inhibitors of CYP3A[a]	Strong Inducers of CYP3A[d]
boceprevir	carbamazepine[d]
cobicistat[a]	Enzalutamide[e]
conivaptan[a]	mitotane
danoprevir and ritonavir[b]	Phenytoin[f]
elvitegravir and ritonavir[b]	rifampin[g]
grapefruit juice[c]	St. John's wort[h]
indinavir and ritonavir[b]	
itraconazole[a]	
ketoconazole	
lopinavir and ritonavir[a,b]	
paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)[b]	
posaconazole	
ritonavir[a,b]	
saquinavir and ritonavir[a,b]	
telaprevir[a]	
tipranavir and ritonavir[a,b]	
troleandomycin	
voriconazole	
clarithromycin[a]	
diltiazem[a]	
idelalisib	
nefazodone	
nelfinavir[a]	

a. Inhibitor of P-gp (defined as those increasing AUC of digoxin to ≥1.25-fold).
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. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).
d. Strong inducer of CYP2B6, CYP3A, and moderate inducer of CYP2C9
e. Strong inducer of CYP3A and moderate inducer of CYP2C9, CYP2C19, CYP3A.
f. Strong inducer of CYP2C19, CYP3A, and moderate inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9.
g. Strong inducer of CYP3A and moderate inducer of CYP1A2, CYP2C19.
h. 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 study physician of the protocol.

Source:

FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#inVivo)

Appendix F Cases of Civil Crisis, Natural Disaster, or Public Health Crisis, including COVID-19 Outbreak

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 SARS-CoV-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 sponsor.

F 1 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 the procedures described in Section F 3. 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.

F 2 Telemedicine Visit to Replace On-site Visit (Where Applicable)

In this appendix 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, drug administration and survival information etc.to be reported and documented.

F 3 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 in the source documents, or by the participant themselves.

F 4 COVID-19 Risk Assessment

The safety of participants is of primary importance. Any potential risks of participating in the study, particularly with the added challenges due to COVID-19 outbreak, should be weighed

against the anticipated benefit (see also principle 2.2 of ICH GCP). Investigators are advised to use clinical judgment in determining infection prevention precautions for study participants.

The emergence of SARS-CoV-2 presents a potential safety risk for participants. Participants enrolling in this study may require more frequent visits to the site for study treatment administration and for study assessments compared to participants receiving standard of care. Therefore, several risk mitigation factors have been implemented related to study conduct during the COVID-19 outbreak, for patient management in an event of COVID-19, and actions to be taken on study treatment (see Section F 6). With these measures in place, it is considered that the anticipated potential benefits for the participants enrolled in this study outweigh the potential risks. All implemented measures prioritise trial participant safety and data validity; in case these two conflict with each other, trial participant safety should always prevail (see also European Medicines Agency Guidance on the management of clinical trials during the COVID-19 [coronavirus] pandemic [EMA 2020]).

F 5 Potential Risks during COVID-19

Every effort should be made to follow the CSP. Section F 7 provides a dose modification and management plan for participants with confirmed or suspected COVID-19 who are being treated with study intervention Acalabrutinib. The risk-benefit assessment should be carefully considered for each participant enrolling in the study based on the known safety risks related to COVID-19, individual needs, and local guidelines and restrictions. Investigators must continue to use their best clinical judgment in determining the most optimal care for participants and utmost diligence in determining their eligibility for study participation, continued study treatment, and overall assessment of benefit/risk of study treatment or participation.

The sponsor must be promptly notified of a site's inability to perform study activities due to COVID-19 outbreak in order to minimise any potential risks.

F 6 Study Treatment Administration

If an AE or SAE is associated with COVID-19, the investigator should determine whether the participants' treatment with investigational product should continue, be interrupted, or be discontinued in accordance with the CSP.

AEs, SAEs, cycle delays and/or treatment suspensions associated with COVID-19 along with logistical issues should be reported according to the eCRF Completion Guidelines.

For dosing discontinuations, where applicable, the dosing discontinuation guidelines should be followed, and the End of Treatment Form(s) completed

F 7 Ongoing Participants

Participants receiving study intervention should continue to undergo safety assessments prior to dosing in accordance with the CSP. In case it is not feasible to perform safety assessments, study intervention should be interrupted until such assessments can be completed.

F 8 If a Participant has an Event Suspected to be COVID-19

Delay or omit study intervention as appropriate and test for COVID-19 per local health authority or institutional guidance.

- Signs and symptoms of COVID-19 include but are not limited to new onset of fever, new or worsening cough, shortness of breath, difficulty breathing and sometimes abnormal chest imaging.
- If COVID-19 is ruled out, study intervention may be resumed per the CSP.
- If COVID-19 **is confirmed or diagnosis still suspected after evaluation**, manage COVID-19 per local guidance until full recovery.

F 9 Participants with Confirmed COVID-19

Participants with confirmed COVID-19 (by local laboratory testing and/or combination of key symptoms) should have study intervention withheld and COVID-19 managed per local guidance.

F 10 Restarting Study Intervention

Study intervention must not be resumed until recovery from COVID-19 (eg, confirmed by imaging, lab testing and/or absence of symptoms) and COVID-19-specific treatment has been completed per local guidance.

The study clinical lead should be contacted if any additional guidance or clarification is needed.

F 11 Vaccination Against COVID-19

Protocol restrictions applying to live attenuated vaccines are relevant for live attenuated COVID-19 vaccines as well. Investigators should apply their discretion assessing the risk-benefit of other types of COVID-19 vaccines for participants in clinical trials. Ideally, administration of the vaccine should be done on a different day other than the day of study drug administration to differentiate any potential AEs seen from the vaccine and study drug. The administration of the vaccine and any potential AEs associated with the vaccine are to be documented on the concomitant medication and AE eCRFs, respectively.

F 12 References

EMA 2020
EMA, Clinical Trials Facilitation and Coordination Group, European Commission. Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic, Version 2, 27 March 2020. Available from: URL: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf. Accessed: 17 December 2020.

Appendix G Abbreviations

Abbreviation or special term	Explanation
5PS	5-point scale
AE ALC	Adverse event Absolute lymphocyte count
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUCinf	Area under the plasma concentration-time curve (from zero to infinity)
AUC0-12	Area under the plasma concentration-time curve (from zero to 12 hours)
AUClast	Area under the plasma concentration-time curve (from zero to the time of the last quantifiable concentration)
AUCτ	Area under the plasma concentration-time curve across the dosing interval; e.g. For BID dosing, AUC0-12 is the AUCτ after single dose
BCR BICR	B-cell receptor Blinded Independent Central Review
BID	Twice daily
BTK	Bruton's tyrosine kinase
CBC	Complete blood count
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practices
CLL	Chronic lymphocytic leukemia
CL/F	Apparent total body clearance of drug from plasma after extravascular administration
Cmax	Maximum observed plasma drug concentration
CR	Complete response
CR	Complete remission (response)
CRi	CR with incomplete marrow recovery
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DLBCL	diffuse large B-cell lymphoma
DILI	Drug-induced liver injury
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid

Abbreviation or special term	Explanation
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Co-operative Oncology group
eCRF	Electronic Case Report Form
EGFR	Epidermal Growth Factor Receptor
EoT	End of Treatment
FDA	Food and Drug Administration
FDG	[^{18}F]fluorodeoxyglucose
FL	Follicular lymphoma
GCP	Good Clinical Practice Unless otherwise noted, 'GCP' shall mean 'the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice' (ICH GCP) and the Japanese 'Good Clinical Practice for Trials on Drugs (Ministry of Health, Labour and Welfare [MHLW] Ordinance No. 28, 27 March 1997, partially revised by MHLW Ordinance and their related notifications' (GCP Ordinance).
GI	Gastrointestinal
G-CSF	granulocyte colony-stimulating factor
GELF	Groupe d'Etude des Lymphomes Folliculaires
anti-HBc	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HNSTD	Highest non-severely toxic dose
HR	Hazard ratio
IB	Investigator Brochure
IATA	International Airline Transportation Association
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IHC	immunohistochemistry
IRB	Institutional Review Board

Abbreviation or special term	Explanation
IRC	Independent Review Committee
IRT	Interactive Response Technology
IMP	Investigational Medicinal Product
iNHL	indolent non-Hodgkin lymphoma
IVIG	Intravenous immunoglobulins
IWCLL	International Workshop on Chronic Lymphocytic Leukaemia
LDH	lactate dehydrogenase
LDi	longest transverse diameter of a lesion
λz	Terminal elimination rate constant
MCL	Mantle Cell Lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
Metabolite: Parent ratio (AUC)	Metabolite: Parent ratio; AUC(metabolite)/AUC(parent)
Metabolite: Parent ratio (Cmax)	Metabolite: Parent ratio; Cmax(metabolite)/ Cmax(parent)
NDA	New Drug Application
NHL	Non-Hodgkin lymphoma
NK	Natural Killer
NIMP	Non Investigational Medicinal Product
nPR	Nodular partial response
OAE	Other significant adverse events
ORR	Overall response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progression of disease
PE	Physical exam
PET	positron-emission tomography
PFS	Progression free survival
PI3K	phosphoinositide-3 kinase
PK	Pharmacokinetics
PML	Progressive Multifocal Leucoencephalopathy
PPD	cross product of the LDi and perpendicular diameter
PR	Partial response

Abbreviation or special term	Explanation
PR	Partial remission (response)
PRL	partial response with lymphocytosis
PS	Performance Status
QD	once per day (dosing)
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
Rac AUC	Accumulation ratio calculated as AUCτ(steady state)/AUCτ(first dose)
Rac Cmax	Accumulation ratio calculated as Cmax,ss(steady state)/Cmax(first dose)
RR	The time between corresponding points on 2 consecutive R waves on ECG
R/R	relapsed/refractory
RTSM	Randomization and Trial Supply Management
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SDi	shortest axis perpendicular to the LDi
SoA	Schedule of Activities
sIFE	Serum immunofixation electrophoresis
SLL	Small Lymphocytic Lymphoma
SPEP	Serum protein electrophoresis
SRC	Safety Review Committee
SPD	sum of the product of the perpendicular diameters for multiple lesions
SUSAR	Suspected unexpected serious adverse reaction
t½λz	Half-life associated with terminal slope (λz) of a semilogarithmic concentration-time curve
NK cell	Natural killer cell
TCP	Temporal change parameter in systemic exposure (also known as: time dependency, temporal parameter change, linearity index); calculated as AUCτ(steady state)/AUCinf(first dose)
TEAE(s)	Treatment-emergent adverse events
tmax	Time to reach maximum observed concentration
TTR TTNT	Time to response Time to next treatment
ULN	Upper limit of normal

Abbreviation or special term	Explanation
Vz/F	Volume of distribution (apparent) following extravascular administration (based on terminal phase)
WBDC	Web Based Data Capture
WHO	World Health Organization

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Document Title:	D8220C00007 Clinical Study Protocol version 7	
Document ID:	Doc ID-003823001	
Version Label:	12.0 CURRENT LATEST APPROVED	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
15-Feb-2023 22:13 UTC	PPD	Content Approval
14-Feb-2023 02:30 UTC	PPD	Management Approval
14-Feb-2023 19:34 UTC	PPD	Management Approval
18-Feb-2023 17:45 UTC	PPD	Content Approval

Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.