Clinical Study Protocol

Drug Substance	Acalabrutinib (ACP-196)
Study Code	D822BC00001
Version	5.0
Date	03Apr2024

A Randomized, Multicenter, Open-Label, Phase 3 Study to Evaluate the Efficacy and Safety of Acalabrutinib versus Chlorambucil plus Rituximab in Subjects with Previously Untreated Chronic Lymphocytic Leukemia

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Version History

Version 5.0, 03 Apr 2024	
Section	**Summary of change**
At planned DCO of 03Jan2024 for the interim analysis, the study has reached the primary objective, this amendment is mainly for adapting change after final analysis.	
Table 1,2,3 footnotes, section 8.1.1,section 8.1.2,section 8.1.3, table 11 footnote c, section 8.1.5	Updated assessment description of HBV PCR, MRD, CCI, hematology serum immunoglobulins, β2-macroglobulin, and TBNK, the testings will be performed locally after final analysis.
Section 1.1, figure 1	• Updated study estimated date of last patient completed to Q4 2024; • Updated the duration of study to approximately 54 months; • Updated subject can crosover with investigator-assessed PD with agreement from medical/monitor/study physician after Amendment 5.0. • Updated the interim analysis at the planned DCO of 03 Jan 2024
Table4	Corrected typo error of secondary objectives.
Table 2, figure 1 Section 4.1, section 6.7	Updated eligibility assessment for crossover
Section 4.4	Updated description of end of study definition
Section 7.1.2	Updated the frequency of survival follow up from every 12 weeks to 24 weeks
Table 10	Corrected typo error of ALC-PD definition
Section 8.1.5	Specified CCI are no longer needed after final analysis and Amendment 5.0
Appendix I	Editorial update and correction
Version 4.0, 14 Mar 2023	
Section	**Summary of change**
This amendment is mainly for CSP TransCelerate template CCI update.	
Section 1.1, Table 2, footnote r; Section 8.1.3	Updated assessment description of cytogenetic and genetic molecular prognostic molecules and FISH evaluation to clarify assessment schedule.
Section 4.4	Updated the duration of final analysis to be consistent across the protocol.
Section 6.1.2	Updated for typo error.
Section 8.4.4	Added Drug Abuse and Drug Misuse definition
Appendix A1	Updated "Regulatory and Ethical Considerations", added sub-heading "Regulatory Reporting Requirements for SAEs" and "Regulatory Reporting Requirements for Serious Breaches" and related details.
Appendix B8	Added detailed Drug Abuse and Drug Misuse definition and examples
Version 3.0, 16 May 2022	

Section	Summary of change
All	IRC changed to BICR
All	'Congenital abnormality' changed to 'Congenital anomaly'
Section 1.1, Table 1, Table 2, Table 3	Revise footnote to clarify EOT visit schedule, and update in section 7.1.1
Section 1.2	Updated statistical methods section to reflect study design update
Section 2.2.3	Updated acalabrutinib clinical studies results based on IB version 11.0
Section 2.3.1	Updated acalabrutinib safety profile based on IB version 11.0
Section 4.1.1	Added instruction for study conduct mitigation during study disruptions due to cases of civil crisis, natural disaster, or public health crisis
Section 5.1	Updated inclusion criteria 10 to change male contraception duration after the last dose of rituximab or chlorambucil from '12 months' to '90 days' to shorten the unnecessary long contraception.
Section 6.1.2	Added to describe Arm B treatment
Section 6.5.2 Table 7	Updated Table 7 for 'instructions for coadministration of mild CYP3A inhibitor and strong CYP3A inducer of drugs with Acalabrutinib coadministered drug'
Section 7.1.1	Updated description of EOT visit schedule
Section 7.1.2	Updated definition of subjects who should enter post-treatment disease follow up period
Section 8.2.2	• Updated 'The nervous system examination will include attention to neurologic signs and symptoms of PML' • Added recording and reporting requirements for 'changes from baseline abnormalities' and 'new or worsened clinically significant abnormalities'
Section 8.2.3	• Updated vital signs collection requirement • Added recording and reporting requirements for 'changes from baseline abnormalities' and 'new or worsened clinically significant abnormalities'
Section 8.3.1 and Table 13	Updated time period and frequency for collecting AE and SAE information for clarity and change in reportability for AEs of concern post-30 days last dose.
Section 8.3.10	Updated requirements for AESI reporting
Section 8.4.2.2	Updated male contraception or donating or banking sperm requirement for non-sterilised male subjects to 90 days after the last dose of rituximab or chlorambucil to reflect changes made to section 5.1.
Section 9.2	Updates to trial design as follows: edits to hazard ratio, update to interim and final analyses to accommodate expectation of the hazard ratio given latest acalabrutinib data, related updates in section 9.5.6 and section 9.6.
Section 9.3, Table 16	Update description of outcome variable for efficacy data.
Section 9.5.6	Updates to trial design as follows: edits to hazard ratio, update to interim and final analyses to accommodate expectation of the hazard ratio given latest acalabrutinib data
Section 9.6	Updates to trial design as follows: edits to hazard ratio, update to interim and final analyses to accommodate expectation of the hazard ratio given latest acalabrutinib data

Section 11	Added Appendix J and move Abbreviations to Appendix K.
Appendix J	Added appendix J to give guidance for implementing changes during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis
Version 2.0, 21 October 2020	
Section	**Summary of change**
All	• 'Medical Monitor' changed to 'Study Physician' • 'IVRS/IWRS' changed to 'IRT/RTSM'
Section 1.1, Table 2	Added footnote to clarify MRD assessment schedule
Section 1.2	Updated the study timeline under statistical methods part
Section 2.3.1	Updated acalabrutinib safety profile based on IB version 8.1
Section 3	Clarified definition of overall response rate
Section 4.1	Removed description of crossover procedure, and added a separate section in 6.8
Section 5	• Clarified inclusion criteria 6 • Updated inclusion criteria 10 for highly effective methods of contraception • Updated the inclusion criteria for total bilirubin ≤2.0×ULN to keep consistency with other similar studies. • Rephrased the inclusion criteria of reproduction for female subject to be more understandable
Section 6.5.1	Moved permitted therapy of short course use of steroids (≤2 weeks) >20 mg/day from "6.5.2 Prohibited concomitant therapy" to "6.5.1 Permitted concomitant therapy"
Section 6.5.2	• Updated the management of subject who develop a second primary malignancy while on trial • Added dosing modification guideline for use of moderate/strong inhibitors/ inducers of CYP3A • Clarified use of proton-pump inhibitors, H2 receptor antagonists or antacids while taking acalabrutinib • Updated prohibited medication
Section 6.6	• Corrected acalabrutinib dose modification in Table 7 • Clarifying edits on rituximab dose modification
Section 6.6.1	Rephrased the dose delay and modification section of Acalabrutinib to be more understandable
Section 6.6.2	Rephrased the dose delay and modification section of Rituximab and chlorambucil to be more understandable
Section 6.8	Added the section to clarify the procedure for crossover
Section 8.0	Adjusted sections' order and add more required information regarding AE/SAE collection
Section 8.1.1	• Correction on target lesion selection • Added nPR definition • Added clarification on the process of BICR confirmation of investigator-assessed disease progression • Added clarification on investigator assessment of the overall response with blood lymphocyte count

Section 8.3.2	• Updated AE/SAE reporting requirement after a subject's last visit • Added wording regarding how to follow the CTCAE
Section 8.3.5	Clarified the definition of AEs based on examinations and tests
Section 8.3.8	• Removed new cancer section and combined the related wording with second primary malignancies • Added second primary malignancies
Section 8.3.9	Clarified death handling when death occur after the protocol-defined follow-up period
Section 8.3.11	Added that safety data to be collected following the final data cutoff of the study
Section 8.4.2.2	Added the data collection regarding pregnancy of the participant's partner
Section 8.4.3	Added the overdose handling regarding SoC
Section 9.2	Updated study timeline for the final PFS analysis prediction based on study update timeline
Section 9.4	• Clarified on PFS censor • Added nPR category for the overall response rate
Section 9.5.1.2	Added nPR category for the overall response rate
Section 9.6	Updated anticipated Interim analyses timeline based on study update timeline and IDMC responsibility
Appendix B	• Added a header for the examples of important medical events in section B5 • Rephrased content in section B7 • Removed AE for malignant tumours which is not applicable for study
Appendix D	• Section D4.2, added clarification that investigator should determine PHL criteria were met for the subject • Section D6, added for actions required when potential Hy's law criteria are met before and after starting study treatment • Section D6, added for actions required for repeat episodes of potential Hy's law
Appendix H	Updated examples of co-administered drugs that need additional consideration
Appendix I	Added appendix I to give guidelines for defining tumours lysis syndrome
Version 1.0, 11 July 2019	
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.

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1.1 Schedule of assessments (SoA)

The schedule of assessments (SoA) for Arm A is presented in Table 1.

The SoA for Arm B is presented in Table 2.

The SoA for the crossover arm is presented in Table 3.

Table 1 Schedule of Assessments: Treatment Arm A (Acalabrutinib)

	Screening	Treatment [a] and Post-treatment Disease Follow-up Phase [b]										EoT/SFU Visit [c]	Survival Follow up	Details in Section
Days		**Cycle 1 (28-day cycle)**				**Cycle 2 (28-day cycle)**			**Cycles 3-7 (28-day cycles)**	**q12 weeks starting at Cycle 10 (e.g., Cycles 10, 13, 16)**	**Response evaluation assessed Cycle 1–25: q12 wks After C25: q24 wks [d]**		**Q24 weeks ***	
		1	**8**	**15**	**22**	**1**	**8**	**15**	**1**					
Visit window	−28 days	±3 days				±3 days			±3 days	±3 days	±14 days	+7 days	±7 days	
Study drug administration														
Arm A Acalabrutinib 100 mg BID PO		Continuous twice daily dosing												4.3.1
Dispense/return of drug		X				X			X	X				6.4.1
Drug accountability		X	X	X	X	X	X	X	X	X				6.2, 6.4
Routine clinical procedures														
Informed consent	X													5.1, A 3
Confirm eligibility and randomize	X													4.1, 5, 6.3
Medical history (incl. Rai stage)	X													8
CIRS	X													Appendix F
Physical exam	X	X				X			X	X	X	X		8.2.2
Vital signs	X	X	X	X	X	X	X	X	X	X		X		8.2.3
Weight	X	X				X			X	X		X		8.2.2

	Screening	Treatment [a] and Post-treatment Disease Follow-up Phase [b]										EoT/SFU Visit [c]	Survival Follow up	Details in Section
Days		**Cycle 1 (28-day cycle)**				**Cycle 2 (28-day cycle)**			**Cycles 3-7 (28-day cycles)**	**q12 weeks starting at Cycle 10 (e.g., Cycles 10, 13, 16)**	**Response evaluation assessed Cycle 1–25: q12 wks After C25: q24 wks [d]**		**Q24 weeks ***	
		1	**8**	**15**	**22**	**1**	**8**	**15**	**1**					
Visit window	–28 days	±3 days				±3 days			±3 days	±3 days	±14 days	+7 days	±7 days	
Concomitant medications	X	←═══									→═══	X		6.5
ECOG PS	X	X				X			X	X		X		8.2.5
Routine safety measurements														
ECG	X													8.2.4
Hepatitis serology [e]	X													5.2, 8.1.3
Adverse events [f]	X	←═══									→═══	X	SAEs only	8.3, 8.4
Pregnancy test [g]	X	X	As clinically indicated									X		8.1.3, 8.4.2
HBV PCR [h]*	X					X			QM	Q3M*			Q3M*	8.1.3
HCV PCR [i]	X													8.1.3
Clinical chemistry	X	X[j]		X		X		X	X	X		X		8.1.3
Efficacy measurements														
CT scans [k]	X[l]								Cycles 4, 7 only		Every 24 weeks after Cycle 7			8.1.1
Overall response assessment											X			3, 9.4.1.2
Bone marrow biopsy and aspirate	X[m]										To confirm CR[n]			8.1.1

	Screening	Treatment [a] and Post-treatment Disease Follow-up Phase [b]										EoT/SFU Visit [c]	Survival Follow up	Details in Section
Days		**Cycle 1 (28-day cycle)**				**Cycle 2 (28-day cycle)**			**Cycles 3-7 (28-day cycles)**	**q12 weeks starting at Cycle 10 (e.g., Cycles 10, 13, 16)**	**Response evaluation assessed Cycle 1–25: q12 wks After C25: q24 wks [d]**		**Q24 weeks ***	
		1	**8**	**15**	**22**	**1**	**8**	**15**	**1**					
Visit window	–28 days	±3 days				±3 days			±3 days	±3 days	±14 days	+7 days	±7 days	
MRD assessment [o]*	X [m] (PB and BM)									Cycle 9 only (PB only)	At PR, CR, and CRi (PB and BM)	X (PB and BM)		8.1.2
CCI														
Disease-related symptoms	X					X			X	X	X			8.1.4
Hematology [r]*	X	X [j]	X	X	X	X	X	X	X	X	ANC, ALC, PLT, Hgb (within CT ±7days) *	X		8.1.3
Survival status and new anticancer therapy													X	7.1.2
Other assessments														
Cytogenetics and genetic molecular prognostic molecules*	X											EoT or SFU [s]*		8.1.3

	Screening	Treatment [a] and Post-treatment Disease Follow-up Phase [b]										EoT/SFU Visit [c]	Survival Follow up	Details in Section
Days		**Cycle 1 (28-day cycle)**				**Cycle 2 (28-day cycle)**			**Cycles 3-7 (28-day cycles)**	**q12 weeks starting at Cycle 10 (e.g., Cycles 10, 13, 16)**	**Response evaluation assessed Cycle 1–25: q12 wks After C25: q24 wks [d]**		**Q24 weeks ***	
		1	**8**	**15**	**22**	**1**	**8**	**15**	**1**					
Visit window	–28 days	±3 days				±3 days			±3 days	±3 days	±14 days	+7 days	±7 days	
Serum immunoglobulins, β2-microglobulin [t], T/B/NK counts [t*]		X [j]							Cycle 7 only	Every 24 weeks (e.g., Cycles 13, 19) [q*]				8.1.3
PK sample collection [u]						X								8.5
FISH panel*	X								Cycle 7 only [v]			EoT or SFU [s*]		8.1.3

Abbreviations: ALC=absolute lymphocyte count; ANC=absolute neutrophil count; BID=twice daily; BM=bone marrow; CIRS=Cumulative Illness Rating Scale; CR=complete remission (response); CT=computed tomography; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group performance status; EoT=end of treatment; FISH=fluorescence in situ hybridization; HBc=hepatitis B core antibody; HBs=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; Hgb=hemoglobin level; IVIG=intravenous immunoglobulins; MRD=minimal residual disease; PB=peripheral blood; PCR=polymerase chain reaction; PK=pharmacokinetics; PLT=platelet count; PO=oral; CCI [redacted]; QM=every month; SFU=safety follow up.

*As of Amendment 5.0

a. There is no restriction on maximum treatment allowed with acalabrutinib.

b. For subjects who discontinue study drug due to reasons other than 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 12 weeks or 24 weeks from the date of last disease evaluation until disease progression, regardless of whether the subject receives a new anticancer therapy.

c. An end of treatment visit will be done within 7 days for subjects who permanently discontinue study drug early for any reason (except for death, lost to follow-up, or withdrawal of consent), including disease progression. See detail in Section 7.1.1. A safety follow-up visit is conducted 30 days (+7 days) after the last acalabrutinib dose, regardless of whether the subject receives a new anticancer therapy or demonstrates disease progression within this timeframe. If the safety follow-up visit is within ±7 days of a regularly scheduled visit during the post-treatment phase, the visits may be combined into a single visit.

d. Response evaluations will be done every 12 weeks (±14 days) with the first on-treatment assessment occurring on Cycle 4 Day 1, the second on Cycle 7 Day 1, and so on through Cycle 25. After Cycle 25 response evaluations will be done every 24 weeks (±14 days) thereafter, until disease progression. For additional details on the confirmatory bone marrow biopsy for subjects in Arm A, see Minimal Residual Disease/Response Evaluation in Section 8.1.2.

e. Hepatitis serology must include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B core antibody (anti-HBc), and hepatitis C (HCV) antibody.
f. After the end of the protocol-defined adverse event reporting period (Section 8.3.1), only serious adverse events considered related to study drug(s) or study procedures are required to be collected.
g. 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.
h. Subjects who are anti-HBc positive should have a quantitative PCR test for HBV DNA performed during screening and every 3 months thereafter. Monitoring every 3 months 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 HBV. As intravenous immunoglobulins (IVIG) may cause false-positive hepatitis serology, monthly PCR testing is not required in subjects who are currently receiving or who have 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).
i. Subjects with a known history of hepatitis C or who are HCV 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.
j. The indicated samples at this timepoint (Cycle 1 Day 1) must be drawn predose. If screening assessments chemistry and hematology are performed within 5 days prior to Cycle 1 Day 1, they do not need to be repeated at Cycle 1 Day 1.
k. CT scan can be performed up to 7 days before response evaluation.
l. Subjects who have standard of care CT/MRI results may use these results in lieu of the Screening CT/MRI required for this study, provided the CT/MRI was done within 28 days of first dose and was acquired in accordance with the guidelines outlined in Section 8.1.1.
m. Bone marrow aspiration and biopsy will be done at screening or within 60 days before the first dose of study drug per clinical guidelines. Bone marrow biopsy and aspirate, MRD assessment can be tested on Cycle 1 Day 1 pre-dose if not performed during screening.
n. If the subject's physical examination findings, laboratory evaluations, and radiographic evaluations suggest that CR has been achieved, a confirmatory bone marrow aspirate/biopsy must be obtained to confirm the CR.
o. If the subject's physical examination findings, laboratory evaluations, and radiographic evaluations suggest that PR, CR, or CRi has been achieved, a peripheral blood (PB) and bone marrow (BM) sample to evaluate MRD status (flow based) should be done between 8-12 weeks from the time of supportive clinical assessments, including CT imaging of suspected PR, CR, or CRi. If MRD samples are not taken at EoT visit, the samples can be drawn at SFU visit. After final analysis(FA) and per Amendment 5.0, MRD tests are not mandatory and will be locally performed per clinical practice.
p. CCI [redacted]
q. After Cycle 7 Day 1, CCI [redacted] serum immunoglobulins, β2-microglobulin, and T/B/NK counts should be collected every 24 weeks, beginning with Cycle 13. After FA and per Amendment 5.0, CCI [redacted] are not required, laboratory assessments including serum immunoglobulins, β2-microglobulin, and T/B/NK are not required and will be locally performed if necessary per the discretion of investigator.
r. Hematology assessments also conducted as part of safety activities. After FA and per Amendment 5.0, hematology testing will be performed locally.
s. Blood sample for Cytogenetics and genetic molecular prognostic molecules, FISH evaluation will also be drawn when a subject has a disease-progression, at the end of treatment visit or a safety follow-up visit. After FA and per Amendment 5.0, Cytogenetics and genetic molecular prognostic molecules and FISH are not required and will be locally performed per the discretion of investigator.
t. β2-microglobulin and T/B/NK to be analyzed by central laboratory. After FA and per Amendment 5.0, β2-microglobulin and T/B/NK are not required and will be locally performed per the discretion of investigator.
u. Sparse PK sampling will occur on Cycle 2 Day 1. For subjects where in PK sampling could not be done on Cycle 2 Day 1 and can be done on Cycle 3 Day 1 instead. On the day of sampling, the subject will not take a dose before arrival at the clinic. The dose will be observed by clinic staff and the time of dose will be recorded. PK samples will be collected predose (within 30 minutes before the morning dosing) and post-dose at the following timepoints: 1 hour (± 15 minutes) post-dose, 2 hours (±15 minutes) post-dose, and 4 hours (± 30 minutes) post-dose.
v. If these samples are damaged during collection or shipment, they should be redrawn at any subsequent visit.

Table 2 Schedule of Assessments: Treatment Arm B (Rituximab and Chlorambucil)

		Screening	Treatment Phase										Post-treatment Disease Follow-up Phase [a]		Treatment and Post-treatment Disease Follow-up Phase	EoT/ SFU Visit [b]	Survival Follow up	Details in Section
Days			Cycle 1 (28-day cycle)					Cycle 2 (28-day cycle)			Cycles 3-6 (28-day cycles)		Cycle 7 (28-day cycle)	q12 weeks starting at Cycle 10 (e.g., Cycles 10, 13, 16)	Response evaluation assessed Cycle 1–25: q12 wks After C25: q24 wks [c]		Q24 weeks *	
			1	2	8	15	22	1	8	15	1	15	1					
Visit window		–28 days	±3 days					±3 days			±3 days		±3 days	±3 days	±14 days	+7 days	±7 days	
Study drug administration																		
Arm B	Rituximab IV 375 mg/m^2		X															4.3.2
	Rituximab IV 500 mg/m^2							X			X							4.3.2
	Chlorambucil 0.5 mg/kg PO		X			X		X		X	X	X						4.3.3
Dispense/return of drug			X			X		X		X	X	X						6.4
Drug accountability			X			X		X		X	X	X						6.2, 6.4
Routine clinical procedures																		
Informed consent		X																5.1, A 3
Confirm eligibility and randomize		X																4.1, 5, 6.3

	Screening	Treatment Phase										Post-treatment Disease Follow-up Phase [a]		Treatment and Post-treatment Disease Follow-up Phase	EoT/ SFU Visit [b]	Survival Follow up	Details in Section
Days		Cycle 1 (28-day cycle)					Cycle 2 (28-day cycle)			Cycles 3-6 (28-day cycles)		Cycle 7 (28-day cycle)	q12 weeks starting at Cycle 10 (e.g., Cycles 10, 13, 16)	Response evaluation assessed Cycle 1–25: q12 wks After C25: q24 wks [c]		Q24 weeks *	
		1	2	8	15	22	1	8	15	1	15	1					
Visit window	–28 days	±3 days					±3 days			±3 days		±3 days	±3 days	±14 days	+7 days	±7 days	
Medical history (incl. Rai stage)	X																8
CIRS	X																Appendix F
Physical exam	X	X					X			X		X	X	X	X		8.2.2
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X		X		8.2.3
Weight	X	X			X		X		X	X	X	X	X		X		8.2.2
Concomitant medications	X	←═══													X		6.5
ECOG PS	X	X					X			X		X	X		X		8.2.5
Routine safety measurements																	
ECG	X																8.2.4
Hepatitis serology [d]	X																5.2, 8.1.3
Adverse events [e]	X	←═══													X	SAEs only	8.3, 8.4
Pregnancy test [f]	X	X	As clinically indicated												X		8.1.3, 8.4.2
HBV PCR [g]	X						X			QM		X	QM			QM	8.1.3
HCV PCR [h]	X																8.1.3

	Screening	Treatment Phase										Post-treatment Disease Follow-up Phase [a]		Treatment and Post-treatment Disease Follow-up Phase	EoT/ SFU Visit [b]	Survival Follow up	Details in Section
Days		**Cycle 1 (28-day cycle)**					**Cycle 2 (28-day cycle)**			**Cycles 3-6 (28-day cycles)**		**Cycle 7 (28-day cycle)**	**q12 weeks starting at Cycle 10 (e.g., Cycles 10, 13, 16)**	**Response evaluation assessed Cycle 1–25: q12 wks After C25: q24 wks [c]**		**Q24 weeks ***	
		1	**2**	**8**	**15**	**22**	**1**	**8**	**15**	**1**	**15**	**1**					
Visit window	–28 days	±3 days					±3 days			±3 days		±3 days	±3 days	±14 days	+7 days	±7 days	
Clinical chemistry	X	X [i]	X		X		X		X	X		X	X		X		8.1.3
Efficacy measurements																	
CT scans [j]	X [k]									Cycle 4 only		X		Every 24 weeks after Cycle 7			8.1.1
Overall response assessment														X			3, 9.4.1.2
Bone marrow biopsy and aspirate	X [l]													To confirm CR [m]			8.1.1
MRD assessment [n*]	X [l] (PB and BM)												Cycle 9 only [u] (PB only)	At PR, CR, CRi (PB and BM)			8.1.2
CCI																	
Disease-related symptoms	X						X			X		X	X	X			8.1.4

	Screening	Treatment Phase										Post-treatment Disease Follow-up Phase [a]		Treatment and Post-treatment Disease Follow-up Phase	EoT/ SFU Visit [b]	Survival Follow up	Details in Section
Days		Cycle 1 (28-day cycle)					Cycle 2 (28-day cycle)			Cycles 3-6 (28-day cycles)		Cycle 7 (28-day cycle)	q12 weeks starting at Cycle 10 (e.g., Cycles 10, 13, 16)	Response evaluation assessed Cycle 1–25: q12 wks After C25: q24 wks [c]		Q24 weeks *	
		1	2	8	15	22	1	8	15	1	15	1					
Visit window	–28 days	±3 days					±3 days			±3 days		±3 days	±3 days	±14 days	+7 days	±7 days	
Hematology [q]*	X	X[i]		X	X	X	X	X	X	X		X	X	ANC, ALC, PLT, Hgb (within CT± 7 days) *	X		8.1.3
Survival status and new anticancer therapy																X	7.1.2
Other assessments																	
Cytogenetics and genetic molecular prognostic molecules*	X														EoT or SFU [r]		8.1.3
Serum immunoglobulins, β2-microglobulin [s], T/B/NK counts [s]*		X[i]										X	Every 24 weeks from Cycle 7 (e.g., Cycles 13, 19) [p]*				8.1.3
FISH panel*	X											Cycle 7 only [t]			EoT or SFU [r]*		8.1.3

Abbreviations: ALC=absolute lymphocyte count; ANC=absolute neutrophil count; CR=complete remission (response); CT=computed tomography; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group performance status; EoT=end of treatment; FISH=fluorescence in situ hybridization; HBc=hepatitis B core antibody; HBs=hepatitis B

surface antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; Hgb=hemoglobin level; IV=intravenous; IVIG=intravenous immunoglobulins; MRD=minimal residual disease; PCR=polymerase chain reaction; PLT=platelet count; PO=oral; CCI ; QM=every month; SFU=safety follow up.

*As of Amendment 5.0

a. Subjects who stop both drugs early because of an adverse event and disease progression has not occurred at that time, will then enter an Post-treatment disease follow up phase. Post-treatment disease follow-up visits should occur approximately every 12 weeks or 24 weeks from the date of last disease evaluation until disease progression, regardless of whether the subject receives a new anticancer therapy.
b. An end of treatment visit will be done within 7 days for subjects who permanently discontinue study drugs early for any reason (except for death, lost to follow-up, or withdrawal of consent), including disease progression. See detail in Section 7.1.1. A safety follow-up visit is conducted 30 days (+7 days) after the last dose of study drug, regardless of whether the subject receives a new anticancer therapy or demonstrates disease progression within this timeframe. If the safety follow-up visit is within ±7 days of a regularly scheduled visit during the Post-treatment Phase, the visits may be combined into a single visit.
c. Response evaluations will be done every 12 weeks (±14 days) with the first on-treatment assessment occurring on Cycle 4 Day 1, the second on Cycle 7 Day 1, and so on through Cycle 25. After Cycle 25 response evaluations will be done every 24 weeks (±14 days) thereafter, until disease progression. For additional details on the confirmatory bone marrow biopsy for subjects in Arm B, see Minimal Residual Disease/Response Evaluation in Section 8.1.2.
d. Hepatitis serology must include hepatitis B surface antigen (HBsAgHbsAg), hepatitis B surface antibody (anti-HBs), hepatitis B core antibody (anti-HBc), and hepatitis C (HCV) antibody.
e. After the end of the protocol-defined adverse event reporting period (Section 8.3.1), only serious adverse events considered related to study drug(s) or study procedures are required to be collected.
f. 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.
g. Subjects who are anti-HBc positive should have a quantitative PCR test for HBV DNA performed during screening and every month thereafter. Monthly 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, monthly PCR testing is not required in subjects who are currently receiving or who have 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).
h. 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.
i. The indicated samples at this timepoint (Cycle 1 Day 1) must be drawn predose. If screening assessments chemistry and hematology are performed within 5 days prior to Cycle 1 Day 1, they do not need to be repeated at Cycle 1 Day 1.
j. CT scan can be performed up to 7 days before response evaluation.
k. Subjects who have standard of care CT/MRI results may use these results in lieu of the Screening CT/MRI required for this study, provided the CT/MRI was done within 28 days of first dose and was acquired in accordance with the guidelines outlined in Section 8.1.1.
l. Bone marrow aspiration and biopsy will be done at screening or within 60 days before the first dose of study drug per clinical guidelines. Bone marrow biopsy and aspirate, MRD assessment can be tested on Cycle 1 Day 1 pre-dose if not performed during screening.
m. If the subject's physical examination findings, laboratory evaluations, and radiographic evaluations suggest that CR has been achieved, a confirmatory bone marrow aspirate/biopsy must be obtained to confirm the CR.
n. If the subject's physical examination findings, laboratory evaluations, and radiographic evaluations suggest that PR, CR, or CRi has been achieved, a peripheral blood (PB) and bone marrow (BM) sample to evaluate MRD status (flow based) should be done between 8-12 weeks from the time of supportive clinical assessments, including CT imaging of suspected PR, CR, or CRi. After FA and per Amendment 5.0, MRD tests are not mandatory and will be locally performed per clinical practice.
o. CCI

p. After Cycle 7 Day 1, [redacted], serum immunoglobulins, β2-microglobulin, and T/B/NK counts should be collected every 24 weeks, beginning with Cycle 13. After FA and per Amendment 5.0, [redacted] are no longer needed, serum immunoglobulins, β2-microglobulin, and T/B/NK are not required and will be locally performed per the discretion of investigator. If MRD samples are not taken at EoT visit, the samples can be drawn at SFU visit.

q. Hematology assessments also conducted as part of safety activities. After FA and per Amendment 5.0, hematology testing will be performed locally.

r. Blood sample for Cytogenetic and genetic molecular prognostic molecules, FISH evaluation will be drawn when a subject has a disease-progression (with PD confirmation from BICR, cytogenetic and genetic molecular prognostic molecules and FISH evaluation need to be performed after signing crossover ICF), at the end of treatment visit or safety follow-up visit. After FA and per Amendment 5.0, cytogenetics and genetic molecular prognostic molecules and FISH are not required and will be locally performed per the discretion of investigator.

s. β2-microglobulin and T/B/NK to be analyzed by central laboratory. After FA and per Amendment 5.0, β2-microglobulin and T/B/NK are not required and will be locally performed per the discretion of investigator.

t. If these samples are damaged during collection or shipment, they should be redrawn at any subsequent visit.

u. For subjects with early termination, samples for MRD assessments maybe collected on the EoT visit.

Table 3 Schedule of Assessments: Crossover

	Screening	Treatment Phase [a]								Treatment and Post-treatment disease follow up Phase [b]		EoT/SFU Visit [c]	Survival Follow up	Details in Section
Days		**Cycle 1 (28-day cycle)**				**Cycle 2 (28-day cycle)**			**Cycles 3-7 (28-day cycles)**	**q12 weeks starting at Cycle 10 (e.g., Cycles 10, 13, 16)**	**Response evaluation assessed Cycle 1–25: q12 wks After C25: q24 weeks [d]**		**Q24 weeks ***	
		1	**8**	**15**	**22**	**1**	**8**	**15**	**1**					
Visit window	–42 days	±3 days				±3 days			±3 days	±3 days	±14 days	+7 days	±7 days	
Study drug administration														
Crossover Acalabrutinib 100 mg BID PO		Continuous twice daily dosing												4.3.1
Dispense/return of drug		X				X			X	X				6.4.1
Drug accountability		X	X	X	X	X	X	X	X	X				6.2, 6.4
Crossover														
Confirm eligibility for crossover	X													4.1
Routine clinical procedures														
Informed consent	X													6.8
Physical exam	X	X				X			X	X	X	X		8.1
Vital signs	X	X	X	X	X	X	X	X	X	X		X		8.2.3
Weight	X	X				X			X	X		X		8.2.2
Concomitant medications	X	←═══→										X		6.5

	Screening	Treatment Phase [a]								Treatment and Post-treatment disease follow up Phase [b]		EoT/SFU Visit [c]	Survival Follow up	Details in Section
Days		**Cycle 1 (28-day cycle)**				**Cycle 2 (28-day cycle)**			**Cycles 3-7 (28-day cycles)**	**q12 weeks starting at Cycle 10 (e.g., Cycles 10, 13, 16)**	**Response evaluation assessed Cycle 1–25: q12 wks After C25: q24 weeks [d]**		**Q24 weeks ***	
		1	**8**	**15**	**22**	**1**	**8**	**15**	**1**					
Visit window	–42 days	±3 days				±3 days			±3 days	±3 days	±14 days	+7 days	±7 days	
ECOG PS	X	X				X			X	X		X		8.2.5
Disease-related Symptoms	X										X			8.1.4
Routine safety measurements														
ECG	X													8.2.4
Adverse events [e]	X	←═══									→═══	X	SAEs only	8.3, 8.4
Pregnancy test [f]	X	X	As clinically indicated									X		8.1.3, 8.4.2
Hepatitis serology [g]	X													5.2, 8.1.3
HBV PCR [h]*	X								Q3M*	Q3M*			Q3M*	8.1.3
HCV PCR [i]	X													8.1.3
Clinical chemistry	X	X [j]		X		X		X	X	X		X		8.1.3
Efficacy measurements														
CT scans [k]	X								Cycle 4, 7 only		Every 24 weeks after Cycle 7			8.1.1
Overall response assessment											X			3, 9.4.1.2

	Screening	Treatment Phase [a]								Treatment and Post-treatment disease follow up Phase [b]		EoT/SFU Visit [c]	Survival Follow up	Details in Section
Days		Cycle 1 (28-day cycle)				Cycle 2 (28-day cycle)			Cycles 3-7 (28-day cycles)	q12 weeks starting at Cycle 10 (e.g., Cycles 10, 13, 16)	Response evaluation assessed Cycle 1–25: q12 wks After C25: q24 weeks [d]		Q24 weeks *	
		1	8	15	22	1	8	15	1					
Visit window	–42 days	±3 days				±3 days			±3 days	±3 days	±14 days	+7 days	±7 days	
Bone marrow biopsy and aspirate	X [l]										To confirm CR [m]			8.1.1
MRD assessment [n]*											At CR, CRi (PB and BM) *			8.1.2
Hematology [o]*	X	X [j]	X	X	X	X	X	X	X	X	ANC, ALC, PLT, Hgb (within CT ±7 days) *	X		8.1.3
Survival status and new anticancer therapy													X	7.1.2

Abbreviations: ALC=absolute lymphocyte count; ANC=absolute neutrophil count; BID=twice daily; CR=complete remission (response); CT=computed tomography; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group performance status; EoT=end of treatment; FISH=fluorescence in situ hybridization; HBc=hepatitis B core antibody; HBs=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; Hgb=hemoglobin level; IVIG=intravenous immunoglobulins; MRD=minimal residual disease; PCR=polymerase chain reaction; PK=pharmacokinetics; PLT=platelet count; PO=oral; CCI ; QM=every month; SFU=safety follow up.

*As of Amendment 5.0

a. There is no restriction on maximum treatment allowed with acalabrutinib.
b. The Post-treatment disease follow up phase begins when the subject stops acalabrutinib due to reasons other than disease progression. Visits should occur approximately every 12 weeks or 24 weeks from the date of last disease evaluation until disease progression, regardless of whether the subject receives a new anticancer therapy.
c. An end of treatment visit will be done within 7 days for subjects who permanently discontinue study drug early for any reason (except for death, lost to follow-up, or withdrawal of consent), including disease progression. See detail in Section 7.1.1. A safety follow-up visit is conducted 30 days (+7) after the last acalabrutinib dose, regardless of whether the subject receives a new anticancer therapy or demonstrates disease progression within this timeframe. If the safety follow-up visit is within ±7 days of a regularly scheduled visit during the Post-treatment Phase, the visits may be combined into a single visit.

d. Response evaluations will be done every 12 weeks (±14 days) with the first on-treatment assessment occurring on Cycle 4 Day 1, the second on Cycle 7 Day 1, and so on through Cycle 25, and then every 24 weeks (±14 days) thereafter. For additional details on the confirmatory bone marrow biopsy for subjects in Arm C, see Minimal Residual Disease/Response Evaluation in Section 8.1.2.
e. After the end of the protocol-defined adverse event reporting period (Section 8.3.1), only serious adverse events considered related to study drug(s) or study procedures are required to be collected.
f. 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.
g. Hepatitis serology must include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B core antibody (anti-HBc), and hepatitis C (HCV) antibody.
h. Subjects who are anti-HBc positive should have a quantitative PCR test for HBV DNA performed during screening and every 3 months thereafter. Monitoring every 3 months 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, 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).
i. Subject 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.
j. The indicated samples at this timepoint (Cycle 1 Day 1) must be drawn predose. If screening assessments chemistry and hematology are performed within 5 days prior to Cycle 1 Day 1, they do not need to be repeated at Cycle 1 Day 1.
k. CT scans that showed disease progression from Arm B can be used for the crossover screening CT scan, if within 60 days of crossover dosing Cycle 1 Day 1. CT scan can be performed up to 7 days before response evaluation.
l. Bone marrow aspiration and biopsy will be done at screening or within 60 days before the first dose of study drug per clinical guidelines.
m. If the subject's physical examination findings, laboratory evaluations, and radiographic evaluations suggest that CR has been achieved, a confirmatory bone marrow aspirate/biopsy must be obtained to confirm the CR.
n. If the subject's physical examination findings, laboratory evaluations, and radiographic evaluations suggest that CR or CRi has been achieved after crossover, a peripheral blood (PB) and bone marrow (BM) sample to evaluate MRD status (flow based) should be done between 8-12 weeks from the time of supportive clinical assessments, including CT imaging of suspected CR or CRi. After FA and per Amendment 5.0, MRD tests are not mandatory and will be locally performed per clinical practice.
o. After FA and per Amendment 5.0, hematology testing will be performed locally.

1.2 Synopsis

International co-ordinating investigator:

PPD

Protocol title:

A randomized, multicenter, open-label, Phase 3 study to evaluate the efficacy and safety of acalabrutinib versus chlorambucil plus rituximab in subjects with previously untreated chronic lymphocytic leukemia

Rationale:

This randomized controlled Phase 3 study in previously untreated subjects with chronic lymphocytic leukemia without del(17p) or TP53 mutation is designed to determine whether treatment with acalabrutinib monotherapy (Arm A) results in a clinically significant improvement in progression-free survival as compared with treatment with rituximab in combination with chlorambucil (Arm B).

Objectives and Endpoints	
Primary objective:	**Endpoint/variable:**
To compare the efficacy of acalabrutinib relative to chlorambucil plus rituximab in subjects with previously untreated chronic lymphocytic leukemia without del(17p) or TP53 mutation	Progression free survival is defined as time from randomization until progression per the International Workshop on Chronic Lymphocytic Leukemia 2018 criteria as assessed by blinded independent central review or death due to any cause
Secondary objectives:	**Endpoints/variables:**
To compare acalabrutinib relative to chlorambucil plus rituximab on overall response rate, duration of response, time to next treatment, and overall survival	• Overall response rate is defined as the proportion of patients who have a complete response, complete response with incomplete bone marrow recovery, nodular partial response or partial response, as determined by blinded independent central review and investigator per International Workshop on Chronic Lymphocytic Leukemia 2018 criteria • Duration of response is defined as the time from the date of first documented response until date of documented progression or death in the absence of disease progression, as determined by blinded independent central review and investigator • Time to next therapy is defined as time from randomization until institution of non-protocol specified treatment for chronic lymphocytic leukemia • Overall survival is the length of time from randomization until the date of death due to any cause

To evaluate minimal residual disease negativity rate	Minimal residual disease negativity rate (peripheral blood) at the start of Cycle 9
To characterize the pharmacokinetics of acalabrutinib and its major metabolite (ACP-5862)	Summarized plasma concentrations of acalabrutinib and ACP-5862 at specified time points Pharmacokinetic parameters by population analyses as appropriate
Safety objective:	**Endpoints/variables:**
To assess the safety and tolerability of acalabrutinib as compared to chlorambucil plus rituximab in subjects with previously untreated chronic lymphocytic leukemia without del(17p) or TP53 mutation	Safety and tolerability will be evaluated in terms of adverse events, vital signs, clinical laboratory, physical examinations, and electrocardiogram Assessments related to adverse events cover • Occurrence/frequency • Relationship to investigational product as assessed by investigator • Common Terminology Criteria for Adverse Events severity grade • Seriousness • Death • Adverse events leading to discontinuation of investigational product • Adverse events leading to dose reduction of investigational product • Adverse events leading to dose delay of investigational product Vital signs parameters include systolic and diastolic blood pressure, and pulse rate, body temperature. Assessments cover • Observed value • Absolute change from baseline values over time
Exploratory objectives:	**Endpoint/variable**:
CCI	[redacted]

Note: Sensitivity analysis of PFS will be performed based on the investigator's assessment according to IWCLL 2018.

Overall design:

This randomized, regional, multicenter, open-label, Phase 3 study will evaluate the efficacy and safety of acalabrutinib monotherapy versus chlorambucil plus rituximab in subjects with

previously untreated CLL without del(17p) or TP53 mutation. Given the different treatment administration schedules and treatment durations, this study will use an open-label design.

Patients will be stratified according to the following criteria:

- Eastern Cooperative Oncology Group performance status (ECOG-PS [0-1 versus 2])
- Rai stage (0-II versus III-IV)

Study period:

Estimated date of first patient enrolled: Q1 2020

Estimated date of last patient completed: Q4 2024

Duration of study: Approximately 54 months including enrollment time.

Number of subjects:

Approximately 150 subjects will be randomized in a 1:1 ratio into 2 arms (n=75 patients each) to receive either acalabrutinib monotherapy (Arm A) or rituximab in combination with chlorambucil (Arm B). It is planned to randomize approximately 75 to 120 patients in total (50% to 80% of total sample size) from China.

Treatments and treatment duration:

Treatment Arm A (acalabrutinib monotherapy):

- All eligible subjects will receive acalabrutinib 100 mg BID until disease progression or any other treatment discontinuation criterion is met.

Treatment Arm B (rituximab in combination with chlorambucil):

- Rituximab: IV infusion on Day 1 of each cycle
  - Cycle 1: 375 mg/m^2
  - Cycles 2-6: 500 mg/m^2
- Chlorambucil: orally at a dose of 0.5 mg/kg body weight
  - Day 1 and Day 15 of each cycle
- Treatment will continue for 6 cycles or until there is disease progression or any other treatment discontinuation criterion is met.

Crossover:

At investigator discretion, subjects randomized to Arm B who have BICR-confirmed disease progression and meet eligibility for crossover will receive treatment with single-agent acalabrutinib at 100 mg BID until disease progression or unacceptable toxicity. After the final

analysis and per Amendment 5.0, subjects can crossover with investigator-assessed PD with agreement from medical monitor/study physician prior to the conclusion of the study.

Data monitoring committee:

An independent data monitoring committee (IDMC) comprising independent experts will be established to review the interim analysis results and safety results periodically if needed (see Section 9.6.1). Following the IDMC meeting, the IDMC will report to the sponsor and may recommend changes in the conduct of the study.

Full details of the IDMC procedures, processes, safety review and interim analyses can be found in the IDMC Charter.

Statistical methods:

The primary objective of the study is to test the following hypothesis:

- **H0:** Blinded independent central review (BICR)-assessed progression-free survival (PFS) of Arm A is the same as Arm B
- **H1:** BICR-assessed PFS of Arm A is not the same as Arm B

Under the exponential model assumptions, the study is expected to randomize approximately 75 subjects per arm (150 patients in total from both arms) with 1:1 randomization ratio. The study is sized to achieve more than 95% power to detect a hazard ratio of 0.333 in PFS (which translates into an improvement in median PFS from 30 months to 90 months) at the 2-sided significance level of 0.05, allowing for one interim analysis conducted at approximately 76% of the target events. The sample size calculation assumes a median PFS of 30 months in Arm B (Michallet et al 2018).

The final analysis of BICR-assessed PFS is event-driven and will be conducted when enrollment is completed and there are approximately 50 BICR-assessed PFS events in total from Arm A and Arm B. The accrual period is assumed to be approximately 30 months. It is assumed that about 5% of the patients in each arm will drop out at the time of final PFS analysis. The interim and final analysis are anticipated to occur approximately 40 months and 53 months, respectively, after the first patient is randomized.

One interim analysis will be conducted to assess early efficacy of Arm A versus Arm B with respect to the primary efficacy endpoint, BICR-assessed PFS using Lan and DeMets spending function with O'Brien-Fleming boundary (Lan and DeMets 1983; O'Brien and Fleming 1979). The interim analysis will occur when approximately 38 BICR-assessed PFS events (76% of target PFS events required for final analysis) have been observed in both arms combined. The nominal alpha level for the interim and final analysis of 38 and 50 BICR-assessed PFS events is 0.02 and 0.044 respectively. The actual nominal alpha level

will be determined based on the number of BICR-assessed PFS events observed at the time of each respective analysis.

At DCO of 03Jan2024 for the planned interim analysis, 48 PFS events were observed by BICR which met the criteria of final analysis(approximately 50 events), therefore this analysis was considered as final analysis, hence the study was unblinded.

EAST 6.5 was employed to conduct the sample size calculation.

Efficacy data will be summarized and analyzed using the intent-to-treat (ITT) population (all randomized patients) and the treatment groups will be compared on the basis of randomized treatment, regardless of the treatment actually received. Patients who were randomized but did not subsequently go on to receive study treatment are included in the ITT population.

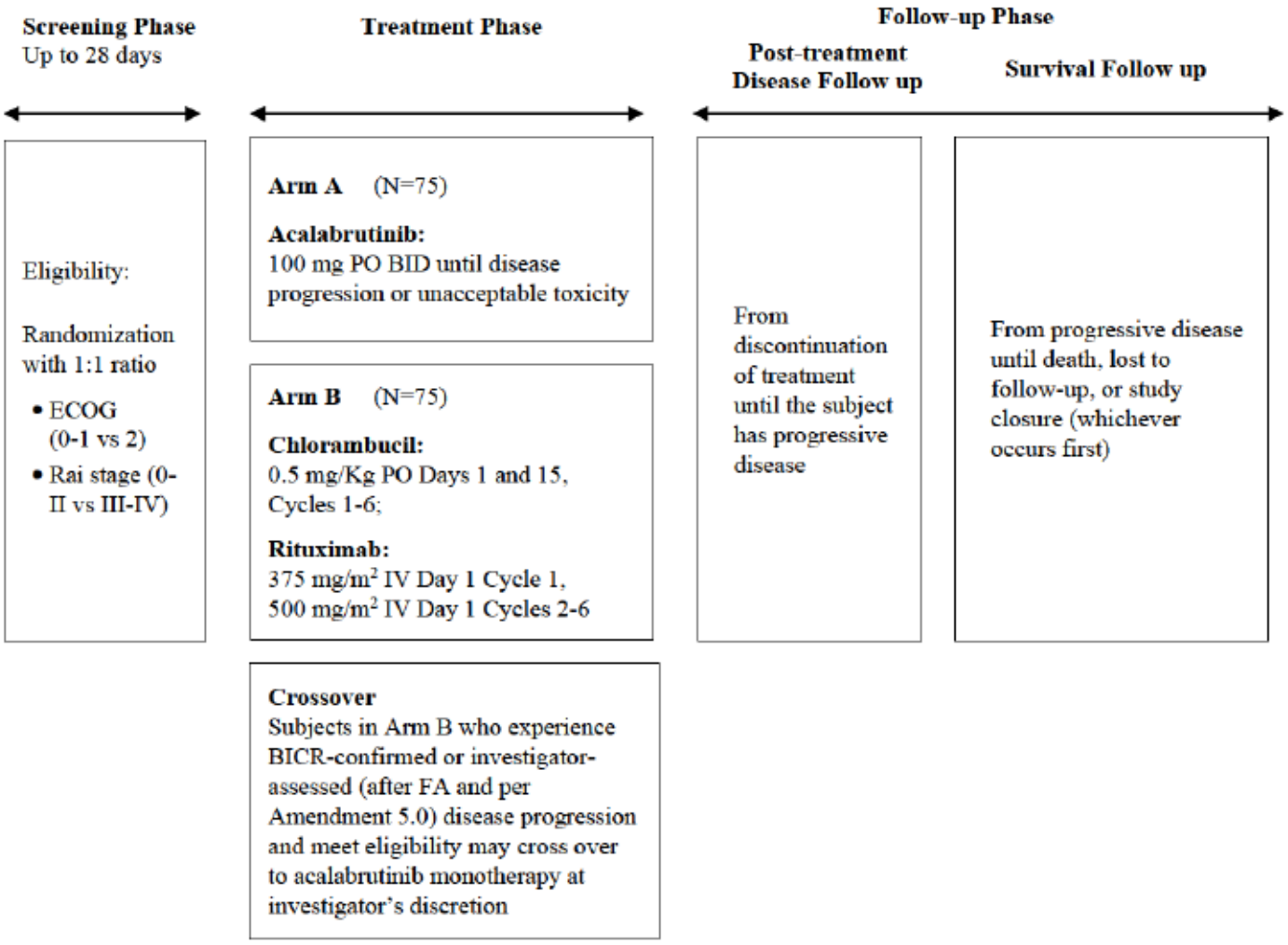
PFS will be defined as time from randomization to the first occurrence of disease progression or death from any cause (whichever occurs first) according to the IWCLL 2018 criteria. The primary analysis will be performed in the ITT population to compare PFS as assessed by the BICR using a 2-sided stratified log rank test, adjusting for ECOG (0-1 versus 2) and Rai stage (0-II versus III-IV) at randomization. The HR and the 2-sided corresponding CI of HR will be estimated using a Cox proportional hazard model stratified by the randomization strata.

All patients who received at least one dose of study drug will be included in the safety analysis set. Safety data will be summarized descriptively and will not be formally analyzed.

1.3 Schema

The general study design is summarised in Figure 1.

Figure 1 Study design



2 INTRODUCTION

2.1 Study Rationale

This study will evaluate the safety and efficacy of the small-molecule BTK inhibitor, acalabrutinib, versus rituximab in combination with chlorambucil in subjects with previously untreated CLL. The design and conduct of this study are supported by an understanding of the natural history and current therapies for subjects with CLL; knowledge of the activity and safety of the BCR inhibitors (i.e., ibrutinib) in subjects with B-cell malignancies; and the available nonclinical and clinical information regarding acalabrutinib.

Rationale for the design of this study is presented in Section 4.2.

2.2 Background

2.2.1 Front line treatment for elderly patients with CLL

Chronic lymphocytic leukemia (CLL) is a malignancy of B cells that predominantly affects the older population. CLL has a variable clinical course, where many patients do not require treatment for years and have survival equal to age matched controls. Other patients, however, exhibit aggressive disease and have a poor prognosis despite appropriate therapy (Byrd 2004). While patients with early disease have not been shown to have a survival advantage with early treatment, most patients will eventually require therapy for their disease with the onset of symptoms or cytopenias. Despite the relatively long life-expectancy for early stage disease, CLL remains an incurable disease.

The treatment of CLL has progressed significantly over the previous decades. While alkylator therapy was used in the past (O'Brien 1995), randomized trials have demonstrated a higher response rate and longer PFS with fludarabine and subsequently with fludarabine- and cyclophosphamide-based combinations in young, fit patients with CLL (Johnson 1996, Rai 2000, Leporrier 2001, Eichhorst 2006, Catovsky 2007, Flinn 2007). At the same time, the chimeric anti-CD20+ monoclonal antibody rituximab was introduced for the treatment of CLL (Byrd 2001, O'Brien 2001). The efficacy of rituximab has been improved by combining it with traditional cytotoxic agents such as fludarabine (Byrd 2003, Byrd 2005) or fludarabine plus cyclophosphamide (Wierda 2005), which have produced high CR rates and extended PFS compared with historical controls. A large randomized clinical trial reported by the German CLL Study Group (GCLLSG) has shown the benefit of the addition of rituximab to fludarabine and cyclophosphamide in PFS and OS in patients with previously untreated CLL (Hallek 2010).

While fludarabine-based chemoimmunotherapy is standard for treatment-naïve, younger/fitter patients with CLL, the therapy for older patients or patients with co-morbidities is less well defined. In the large Phase 2 and Phase 3 trials outlined previously, median ages were typically in the early-60s, while the average age of patients diagnosed with CLL is 72 years,

which calls into question whether these results are generalizable to the entire CLL population. In fact, a randomized Phase 3 trial investigating primary CLL therapy (fludarabine versus chlorambucil) demonstrated that in patients ≥65 years of age, fludarabine was not superior to chlorambucil (Eichhorst 2009). This finding was corroborated by a large retrospective study of front-line trials performed by the Alliance for Clinical Trials in Oncology, which confirmed that fludarabine is not superior to chlorambucil in older patients and also showed that the addition of rituximab to chemotherapy was beneficial regardless of age (Woyach 2013).

The efficacy of CLL treatments in Asian and western patients has been comparable, including chemoimmunotherapy, CD20+ antibodies and BTK inhibitor (Huang 2018). China CLL guideline has been updated in 2018 (Version 2018) and chlorambucil ± rituximab is recommended for first-line unfit patients. Ibrutinib was also approved for the first-line treatment of CLL in China. However, efficacy and safety data of ibrutinib in Chinese CLL population is still very limited, especially in first-line setting.

Currently, trial data that convincingly demonstrate superiority to rituximab and chlorambucil are limited in medically unfit patients, especially in China. There exists a need for frontline chemotherapy-free regimens that can offer improved outcomes with less toxicity.

2.2.2 BTK inhibition in CLL

Bruton tyrosine kinase (BTK) inhibition is an established therapeutic intervention for the treatment of CLL. Ibrutinib (IMBRUVICA®), a covalent BTK inhibitor, has demonstrated improved PFS and OS in patients with CLL as compared with conventional therapies (IMBRUVICA® prescribing information). Although it is a highly potent BTK inhibitor, ibrutinib has also shown in vitro activity against other kinases (e.g., epidermal growth factor receptor [EGFR]; Honigberg et al. 2010). In addition, ibrutinib is a substrate for cytochrome P450 (CYP) enzymes 3A4/5, which increases the possibility of drug-drug interactions. Finally, the inhibition of interleukin-2–inducible T-cell kinase (ITK) that is seen with ibrutinib has the potential to abrogate natural killer (NK) cell antibody-dependent cellular cytotoxicity (Kohrt et al. 2014), which makes combination with monoclonal antibodies less effective.

Zanubrutinib, also known as BGB-3111, is a next generation BTK inhibitor currently in clinical development for CLL and non-Hodgkin lymphoma. Zanubrutinib has a more specific target binding profile than ibrutinib. Zanubrutinib has fewer off-target effects on related enzymes, including EGFR, ITK, Janus kinase 3 (JAK3), human epidermal growth factor receptor 2 (HER2), and tyrosine kinase expressed in hematopoietic carcinoma (TEC). Preliminary data from relapsed/refractory CLL clinical trials showed comparable efficacy and safety profile with ibrutinib (Seymour et al. 2017). A Phase 3 study comparing the frontline use of zanubrutinib versus bendamustine plus rituximab in patients with CLL is currently ongoing.

2.2.3 Acalabrutinib

Acalabrutinib (also known as ACP-196) is a selective, irreversible small molecule inhibitor of BTK currently under clinical investigation. In October 2017, acalabrutinib was granted accelerated approval in the United States (US) for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy.

Acalabrutinib shows encouraging activity and acceptable safety in nonclinical and clinical studies. In addition, laboratory studies have shown that acalabrutinib and its major metabolite ACP-5862 have limited off-target kinase activity, inhibiting only 2 kinases (Erb-B2 receptor tyrosine kinase 4 [ErbB4] and bone marrow tyrosine kinase gene in chromosome X [BMX]) at clinically relevant concentrations (Barf et al. 2017). The lack of activity against other Tec- and Src-family kinases, which are important for the function of T cells, NK cells, and platelets, and against EGFR, a kinase important for epithelial cell functions, may contribute to the safety and efficacy profile of acalabrutinib.

As of 30 October 2021, acalabrutinib has been administered to more than 5000 participants in clinical studies (with approximately 4600 subjects receiving acalabrutinib as monotherapy or in combination with other agents), including subjects with hematologic malignancies, solid tumors, or rheumatoid arthritis, and participants who are healthy subjects or those with mild-to-moderate hepatic impairment.

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

nPR + PR) for acalabrutinib and IR/BR was similar based on BICR assessment (81.3% and 75.5%, respectively) and investigator assessment (79.4% and 83.2%, respectively).

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

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

The effectiveness of acalabrutinib in patients with CLL has also been confirmed in number of supportive studies. See the Acalabrutinib Investigator's Brochure for additional details on nonclinical and clinical studies.

2.3 Benefit/risk assessment

2.3.1 Acalabrutinib

Acalabrutinib monotherapy has demonstrated efficacy in subjects with relapsed/refractory (mantle cell lymphoma) MCL and in subjects with treatment naïve or relapsed/refractory chronic lymphocytic leukemia (CLL).

Based on review of the available safety and efficacy data for acalabrutinib as well as consideration of measures implemented in the acalabrutinib clinical development program to minimize potential risks to subjects, the overall benefit-risk assessment profile of acalabrutinib for the indication under investigation remains favourable for continuing clinical development and is justified by the perceived benefits that may be afforded to the patients.

Precautionary safety measures, and regular monitoring of safety by an independent Data Monitoring Committee (DMC) and the sponsor enable early identification of safety signals in the study and minimize the risk to subjects.

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).

2.3.1.1 Risk assessment

Contraindications

No contraindications are known for acalabrutinib.

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's Brochure.

- **Hemorrhage**
  Serious hemorrhagic events, including fatal events, have occurred in clinical trials with acalabrutinib.

  The mechanism for hemorrhage is not well understood. Patients 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.

- **Infection**
  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 patients 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 specified in the schedule of assessments and as medically appropriate.

  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 patients treated 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 subjects to permanently discontinue study treatment. Continuation of acalabrutinib treatment should be discussed with the study physician.

- **Atrial Fibrillation**

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

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

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.

2.3.2 Rituximab and chlorambucil

Rituximab in combination with chlorambucil is one of the preferred regimens per Chinese CLL/SLL Diagnostic and Treatment Guideline (Version 2018) for medically unfit CLL patients. Risks associated with rituximab and chlorambucil are described in the local prescribing information (i.e., Summary of Product Characteristics, etc).

Overall, the available clinical data including the safety experience support further clinical investigation of acalabrutinib as well as rituximab in combination with chlorambucil in this study. Precautionary safety measures, and regular monitoring of safety by the sponsor enable early identification of safety signals in the study and minimize the risk to subjects.

In conclusion, it is considered that the benefit risk ratio for this study is favorable.

3 OBJECTIVES AND ENDPOINTS

Table 4 Study Objectives

Primary objective:	Endpoint/variable:
To compare the efficacy of acalabrutinib relative to chlorambucil plus rituximab in subjects with previously untreated chronic lymphocytic leukemia without del(17p) or TP53 mutation	Progression free survival is defined as time from randomization until progression per the International Workshop on Chronic Lymphocytic Leukemia 2018 criteria as assessed by blinded independent central review or death due to any cause
Secondary objectives:	**Endpoints/variables:**
To compare acalabrutinib relative to chlorambucil plus rituximab on overall response rate, duration of response, time to next treatment, and overall survival	• Overall response rate is defined as the proportion of patients who have a complete response, complete response with incomplete bone marrow recovery, nodular partial response or partial response, as determined by blinded independent central review and investigator per International Workshop on Chronic Lymphocytic Leukemia 2018 criteria • Duration of response is defined as the time from the date of first documented response until date of documented progression or death in the absence of disease progression, as determined by blinded independent central review and investigator • Time to next therapy is defined as time from randomization until institution of non- protocol specified treatment for chronic lymphocytic leukemia • Overall survival is the length of time from randomization until the date of death due to any cause
To evaluate minimal residual disease negativity rate during treatment and at the end of treatment	Minimal residual disease negativity rate (peripheral blood) at the start of Cycle 9
To characterize the pharmacokinetics of acalabrutinib and its major metabolite (ACP-5862)	Summarized plasma concentrations of acalabrutinib and ACP-5862 at specified time points Pharmacokinetic parameters by population analyses as appropriate

Safety objective:	Endpoints/variables:
To assess the safety and tolerability of acalabrutinib as compared to chlorambucil plus rituximab in subjects with previously untreated chronic lymphocytic leukemia without del(17p) or TP53 mutation	Safety and tolerability will be evaluated in terms of adverse events, vital signs, clinical laboratory, physical examinations, and electrocardiogram Assessments related to adverse events cover • Occurrence/frequency • Relationship to investigational product as assessed by investigator • Common Terminology Criteria for Adverse Events severity grade • Seriousness • Death • Adverse events leading to discontinuation of investigational product • Adverse events leading to dose reduction of investigational product • Adverse events leading to dose delay of investigational product Vital signs parameters include systolic and diastolic blood pressure, and pulse rate, body temperature. Assessments cover • Observed value • Absolute change from baseline values over time
Exploratory objectives:	**Endpoint/variable:**
CCI	

Note: Sensitivity analysis of PFS will be performed based on the investigator's assessment according to IWCLL 2018.

4 Study DESIGN

4.1 Overall design

This randomized, regional, multicenter, open-label, Phase 3 study will evaluate the efficacy and safety of acalabrutinib monotherapy versus chlorambucil plus rituximab in subjects with previously untreated CLL without del(17p) or TP53 mutation.

Approximately 150 subjects will be randomized in a 1:1 ratio into 2 treatment arms (n=75 subjects each) to receive either acalabrutinib monotherapy (Arm A) or rituximab in combination with chlorambucil (Arm B). It is planned to randomize approximately 75 to 120 patients in total (50% to 80% of total sample size) from China. Randomization will be stratified by ECOG [0-1 versus 2] and Rai stage [0-II versus III-IV]. A schedule of screening and trial assessments is provided in Table 1 (Arm A) and Table 2 (Arm B).

At investigator discretion, subjects randomized to Arm B who have BICR-confirmed or investigator-assessed (after FA and per Amendment 5.0) disease progression and meet eligibility for crossover are permitted to receive acalabrutinib monotherapy treatment until disease progression or unacceptable toxicity. For the details, please refer to Section 6.8.

Subject participation will include a screening phase, treatment phase, post-treatment disease follow-up phase, and survival follow-up phase. The screening phase will last up to 28 days before the first dose of study drug, during which the subject's eligibility and baseline characteristics will be determined. The treatment phase will last from randomization until study drug(s) discontinuation. Treatment with acalabrutinib may be continued until disease progression or any other treatment discontinuation criterion is met. Treatment with chlorambucil/rituximab is up to 6 cycles, or until there is disease progression or any other treatment discontinuation criterion is met. Dose modification provisions are provided in Section 6.6.

Assessment for tumor response and progression will be conducted in accordance with the IWCLL 2018 criteria. Disease assessments will be done according to SoA until confirmation of disease progression or death, consent withdrawal, or lost to follow-up. Subjects from Arm B who have BICR-confirmed or investigator-assessed(after FA and per Amendment 5.0) disease progression may be eligible to crossover and receive single agent acalabrutinib 100 mg BID at investigator discretion. An end-of-treatment (EoT) visit is required for safety assessments for any subjects who permanently discontinue study treatment for any reason (except for death, lost to follow-up, or withdrawal of consent), including disease progression. The EoT visit should be performed within 7 days of the last dose of all 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 (SFU) visit.

The survival follow-up will begin after BICR- or investigator-confirmed progressive disease. During this phase, subsequent anticancer therapy to treat CLL including best response, IWCLL indication for treatment initiation, additional malignancy occurrence, and survival status will be recorded. The survival follow-up will continue until death, lost to follow-up, consent withdrawal, or study closure, whichever occurs first. For treatment after the end of study see Section 6.7.

For an overview of the study design see Figure 1, Section 1.3. For details on treatments given during the study, see Section 6 Study Treatments.

For details on what is included in the efficacy and safety endpoints, see Section 3 Objectives and Endpoints.

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 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 Good Clinical Practice, and minimize risks to study integrity.

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

- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened participants. The investigator should confirm this with the designated study physician.
- Home or Remote visit: Performed by a site qualified Health Care Professional (HCP) or HCP provided by a third-party vendor (TPV).
- Telemedicine visit: Remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices. Home delivery of Acalabrutinib by a designated courier. If a site visit is not possible, Acalabrutinib may be delivered to the participant's home by a designated courier if feasible. The option of home delivery ensures a participant's safety in cases of a pandemic where participants may be at increased risk by travelling to the site/clinic. This will also minimize interruption of Acalabrutinib administration during other study

disruptions, eg, site closures due to natural disaster.

- At-home Investigational Product (IP) administration: Performed by a site qualified HCP, or by the participants or the participant's caregiver, if possible. Additional information related to the visit can be obtained via telemedicine.
- Home delivery of Acalabrutinib by a designated courier: If a site visit is not possible, Acalabrutinib may be delivered to the participant's home by a designated courier if feasible. The option of home delivery ensures a participant's safety in cases of a pandemic where participants may be at increased risk by travelling to the site/clinic. This will also minimize interruption of Acalabrutinib administration during other study disruptions, eg, site closures due to natural disaster.

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

4.2 Scientific rationale for study design

This is a Phase 3, randomized, controlled study to assess the benefit/risk profile of acalabrutinib monotherapy versus rituximab in combination with chlorambucil. Given the different treatment administration schedules and treatment durations, this study will use an open-label design.

This study is targeting the medically unfit CLL subjects, and rituximab in combination with chlorambucil was selected as the comparator per Chinese CLL/SLL Diagnostic and Treatment Guideline (Version 2018) as one of the preferred regimens. NCCN Guidelines (Version 5 2019) also recommend chlorambucil plus anti-CD20 monoclonal antibody for frail patients with significant comorbidity (not able to tolerate purine analogs), patients aged ≥65 years, and younger patients with significant comorbidities. Currently, rituximab is the only NCCN-recommended anti-CD20 antibody approved in China.

For CLL patients who are elderly and/or have comorbidities that make them ineligible for fludarabine-based treatment, chlorambucil plus rituximab is an appropriate therapeutic option. In the Phase 2 National Cancer Research Institute Study CLL208, a total of 100 patients were treated with rituximab-chlorambucil, with a median follow-up of 30 months (Hillmen G et al. 2014). Median age of patients was 70 years (range 43 to 86 years), with patients having a median of 7 comorbidities. Overall response rates in the CLL208 study were 84%, with CR achieved in 10% of patients. Median PFS was 23.5 months. Hematologic toxicities accounted for most Grade 3-4 AEs reported, with neutropenia and lymphopenia both occurring in 41% of patients and leukopenia occurring in 23% of patients.

4.3 Justification for dose

4.3.1 Acalabrutinib dose rationale

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 received acalabrutinib at dosages from 100 to 400 mg QD or 100 to 200 mg BID. No dose-limiting toxicities (DLTs) were identified at dosages of ≤400 mg QD or at dosages of 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 (PRL), was 96.9%.

Pharmacodynamics results from ACE-CL-001 suggest BTK re-synthesis 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 (PK)/pharmacodynamics and efficacy results of the Phase 1/2 study, acalabrutinib 100 mg BID is selected as the recommended dose.

In an ongoing Japanese Phase 1 study (CCI [redacted]), preliminary data from Part 1 (the dose-confirmation phase) showed acceptable safety and tolerability. No DLT was observed among the 6 evaluable subjects. No clinically relevant PK ethnic difference was observed between Japanese and Western subjects.

4.3.2 Rituximab dose rationale

The licensed dose of rituximab for use in CLL will be used.

4.3.3 Chlorambucil dose rationale

The rationale for the chlorambucil dosing is based on the findings from the German CLL Study Group (GCLLSG) CLL5 trial (Eichhorst et al, 2009). The trial data indicated that median administered dose for chlorambucil was 0.5 mg/kg and median duration of treatment was 6.5 months, though chlorambucil was scheduled at 0.4 mg/kg initially with a subsequent increase to a maximum of 0.8 mg/kg if well tolerated and on a 14-day cycle for a maximum of 24 cycles in the protocol. The CLL5 study suggested that the treatment schedule of 0.5 mg/kg for 6 cycles in total is a relatively low dose but noninferior to fludarabine in elderly patients with CLL. The same treatment schedule was adopted in the CL-11 study, which demonstrated consistent response and safety profile in the medically unfit CLL patients (Goede et al, 2014).

4.4 End of study definition

The final analysis was conducted approximately 45 months after the first patient was randomized into this study. With Amendment 5.0, the end of study is to occur approximately 54 months after the first subject is randomized into this study.

A subject is considered to have completed the study when he/she has completed his/her last scheduled visit/contact. Subject can withdraw from treatment but may still complete the study by attending all required visits as shown in the SoA.

See Section 6.7 for detailed information for treatment after the end of study. See Appendix A 6 for guidelines for the dissemination of study results.

5 STUDY POPULATION

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

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to assigned/randomised to a study intervention. Under no circumstances can there be exceptions to this rule. Subjects who do not meet the entry requirements are considered screen failures. Screen failure subjects may be rescreened one additional time. (refer to Section 5.4).

In this protocol, "enrolled" subjects are defined as those who sign informed consent and receive an enrollment number. "Randomized" subjects are defined as those who undergo randomization and receive a randomization number.

Where a subject does not meet all the eligibility criteria but is treated in error, or incorrectly started on treatment, the investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the investigator regarding whether to continue or discontinue the patient from treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented. 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 A 3.

Age

3 Men and women:

(a) ≥65 years of age **OR**

(b) >18 and <65 years of age, provided that they meet at least one of the following criteria:

(i) Creatinine clearance 30 to 69 mL/min using the Cockcroft-Gault equation (iwCLL guidelines)

(ii) A score higher than 6 on the Cumulative Illness Rating Score-Geriatric (CIRS-G) (Appendix F)

Type of subject and disease characteristics

4 ECOG performance status of 0, 1, or 2

5 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 B-cell marker (CD19, CD20, and CD23) and CD5

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

(c) Presence of $\geq 5\times10^9$ B lymphocytes/L (5000/μL) in the peripheral blood (at any point since the initial diagnosis)

6 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 absolute lymphocyte count (ALC) obtained at intervals of 2 weeks over an observation period of 2 to 3 months. In subjects with initial blood lymphocyte counts of $<30\times10^9$/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) Symptomatic or functional extranodal involvement (e.g., skin, kidney, lung, spine).

(g) 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

7 Meet the following laboratory parameters:

(a) Adequate bone marrow function independent of growth factor or transfusion support 1 week before assessment, as follows:

(i) Absolute neutrophil count (ANC) ≥750 cells/μL (0.75×10^9/L); ANC ≥500 cells/μL (0.50×10^9/L) in subjects with documented bone marrow involvement of CLL

(ii) Platelet count ≥50,000 cells/μL (50×10^9/L); platelet count ≥30,000 cells/μL (30×10^9/L) in subjects with documented bone marrow involvement of CLL

(b) Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5× upper limit of normal (ULN)

(c) Total bilirubin ≤2.0×ULN, unless directly attributable to Gilbert's syndrome

(d) Estimated creatinine clearance of ≥30 mL/min using the Cockcroft-Gault equation (Appendix E)

Reproduction

8 Negative pregnancy test (urine or serum) for female subjects of childbearing potential prior to enrollment

9 Prior to the planned date of randomization for female subjects, at least 1 of the following criteria should be met:

(a) ≥ 1 year post-menopausal

(b) permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy)

(c) or using highly effective methods of contraception (highly effective methods of contraception are defined in Table 5) for the duration of the study (from the time they sign consent) and for 2 days after the last dose of acalabrutinib or 12 months after the last dose of rituximab or chlorambucil, whichever is longer, to prevent pregnancy.

10 For rituximab and chlorambucil: male subjects who are sexually active must agree to use highly effective methods of contraception with the addition of a barrier method (condom) during the study (from the time they sign consent) and for 90 days after the last dose of

rituximab or chlorambucil, whichever is later, to prevent pregnancy in a partner. Male subjects must agree to refrain from sperm donation during this same time period.

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)
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 and if acceptable to local regulatory agencies and Independent Ethics Committees/Institutional Review Boards. 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 Known detected del(17p) or TP53 mutation (Note: test results should be obtained from central lab during screening)

2 Transformation of CLL to aggressive non-Hodgkin lymphoma (NHL) (e.g., Richter's transformation, PLL, or diffuse large B-cell lymphoma [DLBCL]), or central nervous system (CNS) involvement by leukemia

3 History of confirmed progressive multifocal leukoencephalopathy (PML)

4 History of prior malignancy that could affect compliance with the protocol, or interpretation of results, except for the following:

(a) Curatively treated basal cell carcinoma or squamous cell carcinoma of the skin or carcinoma in situ of the cervix at any time prior to study

(b) Other cancers not specified above which have been curatively treated by surgery and/or radiation therapy from which subject is disease-free for ≥3 years without further treatment

5 Significant cardiovascular disease such as uncontrolled or untreated 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 at Screening. Exception: subjects with controlled, asymptomatic atrial fibrillation during Screening are allowed to enroll on study.

6 Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach, or extensive small bowel resection that is likely to affect absorption, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass

7 Known history of infection with human immunodeficiency virus (HIV)

8 Serologic status reflecting active hepatitis B or C infection

(a) Subjects who are hepatitis B core antibody (anti-HBc) positive and who are hepatitis B surface antigen (HBsAg) negative will need to have a negative polymerase chain reaction (PCR) result before randomization and must be willing to undergo DNA PCR testing during the study. Those who are HbsAg-positive or hepatitis B PCR-positive will be excluded.

(b) Subjects who are hepatitis C antibody positive will need to have a negative PCR result before randomization. Those who are hepatitis C PCR-positive will be excluded.

9 Any active systemic infection (e.g., bacterial, viral, or fungal infection) requiring systemic treatment

10 Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura defined as declining hemoglobin or platelet count secondary to autoimmune destruction within the Screening period

11 History of bleeding diathesis (e.g., hemophilia, von Willebrand disease)

12 History of stroke or intracranial hemorrhage within 6 months before first dose of study drug

13 Major surgical procedure within 30 days of first dose of study drug. 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.

Prior/concomitant therapy

14 Any prior CLL-specific therapies (Note: prior localized radiotherapy is allowed)

15 Corticosteroid use >20 mg/day within 1 week before first dose of study drug, except as indicated for other medical conditions such as inhaled steroid for asthma, topical steroid use, or as premedication for administration of study drug. For example, subjects requiring steroids at daily doses >20 mg prednisone equivalent systemic exposure daily, or those who are administered steroids for leukemia control or white blood cell count lowering are excluded.

16 Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists

17 Requires treatment with a strong CYP3A inhibitor. The use of strong or moderate CYP3A inhibitors or inducers within 7 days of the first dose of study drug is prohibited.

18 Received any investigational drug within 30 days before first dose of study drug

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

20 History of known hypersensitivity or anaphylactic reactions to study drugs or excipients

Prior/concurrent clinical study experience

21 Concurrent participation in another therapeutic clinical trial

Other exclusions

22 For women only: breastfeeding or pregnant

23 Involvement in the planning and/or conduct of the study (applies to both sponsor staff and/or staff at the study site)

24 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

This section is not applicable as no restrictions are required.

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 randomized 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 eCRF (i.e., subject does not meet the required inclusion/exclusion criteria) and register in IRT/RTSM as screen failure.

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened, which requires signing the ICF again and repeating screening procedures. Only 1-time rescreening is allowed in the study. Rescreened participants should be assigned the same participant number (E-code) as for the initial screening. The investigator should discuss each individual case with study physician before any patient is rescreened. The bone marrow biopsy and aspirate, CT scan do not need to be repeated if still within timeframe prior to the

first dose as required in protocol; cytogenetics, genetic molecular prognostic molecules, FISH panel, and MRD do not need to be repeated after confirmation with study physician.

6 STUDY TREATMENTS

Study treatment is defined as any investigational product(s) (IPs [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 or rituximab and chlorambucil.

6.1 Treatments administered

6.1.1 Investigational products

The IP acalabrutinib capsules for oral administration is supplied as 100 mg blue and yellow opaque, hard gelatinous capsules and is provided in white, high-density polyethylene bottles. Labels will be prepared in accordance with Good Clinical Practice (GCP) Ordinance. The drug product is manufactured by AstraZeneca AB. All formulation excipients are compendial and are commonly used in oral formulations

6.1.2 Chlorambucil and Rituximab

Rituximab will be administered as described in Table 6, on Days of Cycles 1 through 6. Locally approved labelling may be considered for administration of rituximab. Chlorambucil will be orally administered at a dose of 0.5 mg/kg of body weight on Days 1 and 15 of Cycles 1 through 6. Chlorambucil should not be dosed sooner than 14 days from the last dose of chlorambucil. On days when chlorambucil and rituximab are both administered, the order of study treatment administration will be chlorambucil followed by rituximab.

The subject's body weight at screening and body surface area (BSA) calculated at screening should be used to calculate the dose of chlorambucil, rituximab throughout the study unless the subject's weight increases or decreases by ≥10% from screening.

Table 6 Study Treatments

	Arm A	Arm B	
Study treatment name:	Acalabrutinib (ACP-196)	Chlorambucil	Rituximab
Dosage formulation:	100 mg capsule for oral administration	As sourced locally	10 mL (100 mg) and 50 mL (500 mg) vial solution for infusion after dilution, 10 mg/mL
Route of administration:	Oral	Oral	IV infusion

Table 6 Study Treatments

	Arm A	Arm B	
Dosing instructions:	One Capsule of 100 mg twice daily orally with approximately 240 mL of water. It may be taken with or without food. The capsule should be swallowed intact and should not be opened or dissolved in liquid. Doses should be administrated approximately 12 hours apart (recommended to be taken as close as the schedule time as possible preferably within ±1 hour). 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. The missed dose will not be made up and must be returned to the site at the next schedule time.	0.5 mg/kg body weight orally on Day 1 and Day 15 of all treatment cycles (Cycles 1-6) Chlorambucil should not be dosed sooner than 14 days from the last dose of chlorambucil. On days when chlorambucil and rituximab are both administered, the order of study treatment administration will be chlorambucil followed by rituximab.	375 mg/m^2 of rituximab IV infusion on Day 1 of the first treatment cycle (Cycle 1). [a] 500 mg/m^2 IV infusion on Day 1 for each of subsequent cycles (Cycles 2-6). Premedicate before each infusion with acetaminophen and an antihistamine in accordance with local prescribing information.
Packaging and labelling	Study treatment will be provided in white, high-density polyethylene bottles. Each bottle will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.	This study will use commercially available chlorambucil. Refer to the approved label of chlorambucil for further detail [b]	This study will use commercially available rituximab. Refer to the approved label of rituximab for further detail [b]
Provider	AstraZeneca AB	Sourced locally by site [b]	Sourced locally by site [b]

[a] The initial dose on Day 1 may be divided for administration to manage IRRs according to local practice.

[b] Chlorambucil and rituximab are sourced locally by site, under certain circumstances when local sourcing is not feasible a standard of care treatment may be supplied centrally through the sponsor, a clinical label will be prepared by the sponsor in such circumstance.

6.2 Preparation/handling/storage/accountability

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. 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 authorised 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 authorised 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).

Further guidance and information for the final disposition of unused study treatment are provided in the Clinical Study Agreement.

6.2.1 Acalabrutinib

No additional preparation and handling are required for acalabrutinib.

6.2.2 Chlorambucil

No additional preparation and handling are required for chlorambucil.

Chlorambucil will be obtained by the investigational sites and labelled locally if required. See local prescribing information for further instructions regarding recommended storage conditions and packaging configuration.

6.2.3 Rituximab

6.2.3.1 Preparation/handling

The antibody is formulated for intravenous injection as a sterile product in a solution of sodium chloride (pH 6.5) containing polysorbate 80 and sodium citrate. Rituximab is packaged in 10 mL (100 mg) and 50 mL (500 mg) pharmaceutical-grade glass vials at a concentration of 10 mg protein per mL.

Rituximab should be stored in a secure refrigerator at 2°-8°Celsius (36°-46°Fahrenheit). Do not freeze or store at room temperature. The product is a protein – HANDLE GENTLY AND AVOID FOAMING, as this may lead to the de-naturing of the product proteins.

All transfer procedures require strict adherence to aseptic techniques, preferably in a laminar flow hood. Prepare rituximab solution as follows:

- Refrigerate (2°-8°C [36°-46°F]) all materials and solutions prior to use.
- Use sterile, non-pyrogenic disposable containers, syringes, needles, stopcocks, and transfer tubing etc.

- Transfer of rituximab from the glass vial should be made by using a suitable sterile graduated syringe and large gauge needle.
- Transfer the appropriate amount of rituximab from the graduated syringe into a partially filed IV pack containing sterile pyrogen-free 0.9% sodium chloride solution (saline solution). Mix by inverting the bag gently. DO NOT USE A VACUUM APPARATUS to transfer the product from syringe to the plastic bag.
- Place an IV administration into the outflow port of the bag containing the infusion solution
- NOTE: DO NOT USE evacuated glass containers which require vented administration sets because this causes foaming as air bubbles pass through the solution.
- The administration of rituximab will be accomplished by slow IV infusion. CAUTION: DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.
- Do not infuse concomitantly with another IV solution or IV medications.

6.2.3.2 Storage

Rituximab should be stored in a secure refrigerator at 2-8°C (36-46°F). Refer to local label for further instruction regarding recommended storage condition.

6.3 Measures to minimise bias: randomisation and blinding

All subjects will be centrally/regional/local assigned to randomised study treatment using an Interactive Response Technology/Randomisation and Trial Supply Management (IRT/RTSM). Before the study is initiated, the telephone number and call-in directions for the IRT and/or the log-in information and directions for the RTSM will be provided to each site.

If a subject withdraws from the study, then his/her enrollment/randomisation code cannot be reused. Withdrawn subjects will not be replaced.

This is an open-label study. To maintain the integrity of the study, AstraZeneca personnel directly involved in the study conduct will refrain from accessing treatment records whenever possible, and under no circumstances will they view data aggregated by treatment arm during the course of the study. The site will contact the IRT/RTSM prior to the start of study treatment administration for each subject. The site will record the treatment assignment on the applicable case report form, if required. Potential bias will be reduced by central randomization. One randomization list will be produced for each of the randomization strata. A blocked randomization will be generated, and all centers will use the same list in order to minimize any imbalance in the number of patients assigned to each treatment group.

6.4 Treatment compliance

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 the sponsor. The investigator or designee is responsible for managing the IMP from time of receipt by the study site until the destruction of all unused IMP at that site. The investigator(s) is responsible for ensuring that all unused IMP is returned to the site by the subject(s).

6.4.1 Acalabrutinib

For acalabrutinib taken in the clinic, subjects should take the dose from the drug dispensed to them for that particular time period. 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. Returned capsules must not be re-dispensed to another subject.

6.4.2 Chlorambucil

Accountability and subject compliance will be assessed by maintaining adequate "drug dispensing" and return records.

Subjects will be asked to return all used and unused chlorambucil containers at the end of the treatment as a measure of compliance.

A Drug Dispensing Log must be kept current and should contain the following information:

- Identification of the subject to whom the study medication was dispensed
- Date(s) and quantity of the study medication dispensed to subject
- Date(s) and quantity of chlorambucil returned by the subject

6.4.3 Rituximab

Subject can only return to site for IV infusion of rituximab. Treatment compliance will be assured by reconciliation of site drug accountability logs.

6.5 Concomitant therapy

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the subject is receiving at the time of 4 weeks prior to starting study treatment and all concomitant treatments during the study through 30 days after the last dose of all study drugs 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

After a subject discontinues study treatment, receipt of all subsequent anticancer therapies to treat CLL will be collected in survival follow-up.

6.5.1 Permitted concomitant therapy

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.

For subjects at risk for infections: bacterial/viral/fungal prophylaxis is allowed per institutional standards.

Short course use of steroids (≤2 weeks) >20 mg/day is permitted for premedication use, or to manage infusion-related reactions or to manage other inflammatory reactions, such as asthma exacerbation. During study participation, subjects may also receive systemic or enteric corticosteroids at any required dosage as needed for treatment-emergent comorbid conditions.

6.5.2 Prohibited concomitant therapy

Any concurrent chemotherapy (e.g., bendamustine, cyclophosphamide, pentostatin, or fludarabine), anticancer immunotherapy (e.g., 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 for treating CLL are prohibited. Localized, short courses of radiotherapy are allowed for the treatment of lesions unrelated to the disease under study, if approved by the study physician. Should a subject develop a second primary malignancy while on trial, the subject should be managed according to institutional guidelines with diagnostic evaluations as clinically indicated, and it may be necessary for subjects to permanently discontinue study treatment. Continuation of acalabrutinib treatment should be discussed with the study physician.

The concomitant use of strong inhibitors/inducers of CYP3A with acalabrutinib should be avoided when possible (see Appendix H). If a subject requires short-term treatment with a strong CYP3A inhibitor (such as anti-infectives for up to 7 days), interrupt acalabrutinib

treatment. Refer to Table 7 for dose modifications due to required short-term use of moderate CYP3A inhibitors.

Warfarin or equivalent vitamin K antagonists (e.g., *phenprocoumon*) are prohibited.

Administration of herbal medication during study treatment period is not recommended, unless it is prescribed by the investigator for treatment of specific clinical events. Use of proton-pump inhibitors, H2 receptor antagonists, or antacids while taking acalabrutinib has the potential to decrease acalabrutinib exposure. If treatment with a gastric acid reducing agent is required, consider using a H2-receptor antagonist (2 hours after acalabrutinib) or antacid (2 hours before or 2 hours after acalabrutinib). Avoid coadministration with proton-pump inhibitors.

Table 7 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.
Mild CYP3A inhibitor	No change
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.
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.

6.5.3 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the subject's safety and wellbeing, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

6.6 Dose delay and modification

6.6.1 Acalabrutinib

The actions in Table 8 should be taken for the following toxicities (according to CTCAE criteria version 5.0):

- 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 decreased in the presence of clinically significant bleeding
- Grade 4 platelets decreased
- 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 8). 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.

Once de-escalation has occurred, the dose should not restart at original dose level.

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.

Table 8 Acalabrutinib Dose Modification

Occurrence	Action
1st-2nd	Hold acalabrutinib until recovery to Grade 1 or baseline; may restart at original dose level (100 mg BID)
3rd	Hold acalabrutinib until recovery to Grade 1 or baseline; restart at one dose level lower (100 mg QD)
4th	Discontinue acalabrutinib.
Abbreviations: BID=twice daily; QD=once per day.	

6.6.2 Rituximab and chlorambucil

If a patient experiences any ≥ Grade 2 non-hematological toxicity, chlorambucil and/or rituximab should be hold until the non-hematological toxicity returns to Grade 1 or baseline. If treatment is delayed for more than 4 weeks due to study drug-related toxicity, chlorambucil and/or rituximab should be discontinued.

If a patient experiences Grade 3 or 4 cytopenia, the guidelines for dose delay (chlorambucil or rituximab) and dose reduction (chlorambucil only) are outlined in Table 9.

Table 9 Rituximab and Chlorambucil Dose Modification

	Chlorambucil	Rituximab
Grade 3 or 4 cytopenia	Delay dosing for a maximum of 4 weeks. Administer G-CSF for neutropenia or platelets or red blood cells as required. 1st episode: If improvement to Grade ≤2 (or baseline), decrease Clb dose to 75% of initial dose for subsequent cycles 2nd episode: If improvement to Grade ≤2 (or baseline), decrease Clb dose to 50% of initial dose for subsequent cycles 3rd episode: Discontinue Clb	If improvement to Grade ≤2 (or baseline), administer full dose. If Clb is discontinued, rituximab may continue at the investigator's discretion.
Grade 1 or 2 cytopenia	No dose reduction or delay	No dose reduction or delay
Abbreviations: Clb=chlorambucil; G-CSF=granulocyte colony-stimulating factor.		

No reduction in the dose of rituximab is allowed. Severe, including fatal, infusion reactions can occur with rituximab. Discontinue rituximab infusion and provide medical treatment for Grade 3 or 4 infusion reactions. For less severe infusion reactions (grade 1 or 2), interrupt the infusion or slow the infusion rate. Rituximab may continue at the discretion of the investigator when the toxicity has improved (Grade ≤2 for hematological toxicity and Grade 1 or baseline for non-hematological toxicity). If rituximab is discontinued, the patient is

withdrawn from study treatment. Refer to the rituximab local prescribing information for dose withholding or discontinuation in response to specific toxicities associated with rituximab.

Chlorambucil dose reductions are described in Table 9. Once reduced, the dose of chlorambucil should not be escalated. A delay of up to 4 weeks is permitted for chlorambucil to allow recovery of hematologic toxicities to Grade ≤2 or non-hematologic toxicities to Grade 1 or baseline level. If the treatment is delayed for more than 4 weeks due to toxicity, chlorambucil should be discontinued.

If a Grade 3 or 4 cytopenia prevents treatment on Day 15 (of any cycle for Arm B), the Day 15 chlorambucil dose will be skipped in order to keep the antibody on schedule. Rituximab + chlorambucil administration on Day 1 of the following cycle will be given if the cytopenia has resolved to Grade ≤2. Chlorambucil will be given at a reduced dose. If the cytopenia persists, rituximab + chlorambucil administration will be delayed until the cytopenia has improved to Grade ≤2

Chlorambucil has been reported to exacerbate or precipitate autoimmune hemolytic anemia and patients should be monitored carefully for this condition. If a rapid decrease of hemoglobin occurs during therapy, the possibility of chlorambucil- or autoantibody-induced hemolysis should be considered and appropriate diagnostic tests (LDH, bilirubin, haptoglobin, reticulocytes, Coombs test) should be performed. If hemolysis is suspected, a Coombs test should be performed. If, in the judgment of the treating physician, there is evidence of clinically significant hemolytic anemia secondary to chlorambucil, study treatment should be promptly withdrawn. Full details of the hemolytic anemia should be recorded on the adverse event pages of the eCRF.

As many of these patients have multiple comorbidities, treatment may be delayed longer than 4 weeks (for both treatments) to enable resolution of unrelated AEs, concurrent diseases, or recovery from surgical procedures. This is at the investigators discretion but should be discussed in advance with the sponsor.

A patient should discontinue study treatment with chlorambucil/rituximab if any of the following occur:

- Grade 4 infusion related symptom (patient should be withdrawn immediately)
- Grade 3 infusion related symptom at re-challenge
- Grade 3 or 4 cytopenia that has not resolved to Grade ≤2 and delays treatment by 4 weeks
- Grade ≥2 non-cytopenic toxicity that does not resolve to Grade 1/baseline and delays treatment by 4 weeks

6.7 Treatment after the end of the study

No intervention for patients is planned after the end of the study. However, provisions will be in place for patients still enrolled at the end of the trial to continue to receive study intervention if, in the opinion of the investigator, they are continuing to receive benefit from treatment.

In the event that a roll-over or safety extension study is available at the time of the database closure, patients currently receiving treatment with study intervention may be transitioned to such a study, and the current study would reach its end. Patients in Arm B will still be allowed to cross over to receive acalabrutinib as specified in section 6.7. The roll-over or safety extension study would ensure treatment continuation with visits and assessments per its protocol. Any patient who would be proposed to move to such a study would be asked to sign a new ICF.

Such subjects who are still receiving or will cross over to receive acalabrutinib will continue to be monitored for all AEs up to 30 (+7) days after the last dose of investigational product. For subjects who do continue to receive treatment beyond the closure of the database, investigators will continue to report all SAEs to the sponsor Patient Safety until 30 days after IP is discontinued, in accordance with Section 8.4.1(Reporting of SAEs).

6.8 Crossover

At investigator discretion, subjects randomized to Arm B who have BICR-confirmed disease progression and meet eligibility for crossover may have the option to receive acalabrutinib monotherapy as crossover treatment provided the informed consent of the crossover treatment is signed. After the final analysis and per Amendment 5.0, subjects can cross over with investigator-assessed PD with agreement from medical monitor/study physician prior to the conclusion of the study.Screening assessments for crossover listed in Table 3 should be performed within the screening time window of 42 days (as the EoT/SFU visit or its corresponding tests in terms of schedule may overlap with the crossover screening visit or its corresponding tests, the EoT/SFU visit and its corresponding tests can be waived in such case, e.g. the tests or assessments are scheduled both in EoT/SFU window and crossover screening window. CT scans that showed disease progression from Arm B can be used for the crossover screening CT scan, if within 60 days of crossover dosing Cycle 1 Day 1). Eligibility for crossover includes the following criteria:

- Crossover candidates must have BICR-confirmed or investigator-assessed disease progression.

- ECOG performance status and the laboratory parameters as outlined in the inclusion criteria #4 and #7, and exclusion criteria #8 should be met. See Section 5.1 and Section 5.2.

- There are no concerns by the investigator judgement including but not limited to safety risks, compliance, restrictions and study process requirements.

Crossover candidates may not receive any other anticancer therapy to treat CLL, including acalabrutinib outside the study, from the last dose of Arm B treatment to the initiation of crossover therapy with acalabrutinib. Should a subject develop a second primary malignancy while on trial, crossover option after curative treatment of the second primary malignancy may be considered after discussion with the study physician. Crossover subjects will be treated with acalabrutinib until disease progression based on investigator assessment or unacceptable toxicity. BICR assessment is not required for crossover subjects.

For crossover subjects, AEs will be collected from time of signature of informed consent of crossover treatment throughout the treatment period and including the follow-up period. The follow-up period is defined as 30 days after the last dose of crossover treatment. The other requirements for AE collection and reporting are provided in Section 8.

7 Discontinuation OF TREATMENT AND SUBJECT Withdrawal

7.1 Discontinuation of study treatment

Subjects may be discontinued from IP 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 discontinued 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 AE that presents a substantial clinical risk to the subject with continued study treatment 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 anti-CLL therapy.
- Study terminated by sponsor.

See the SoA for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed. Subjects that discontinue study treatment will continue with study follow-up visits until death, withdrawal of consent, lost to follow-up, or study termination, whichever occurs first.

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. Patients who have

permanently discontinued from further receipt of IP will need to be discontinued from the IRT/RTSM.

An EoT visit is required for safety assessments for any subjects who permanently discontinue study treatment for any reason (except for death, lost to follow-up, or withdrawal of consent), including disease progression. The end of treatment visit 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. If the SFU visit is within ± 7 days of a regularly scheduled visit during the post-treatment phase, the visits may be combined into a single visit.

In addition to the EoT visit, an SFU visit should be conducted at 30 (+7) days after his or her last dose of all study drugs 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 time frame. Refer to Tables 1-3, for the assessments required for the EoT and SFU visits.

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 subjects enrolled who complete the study treatment (Arm B) or discontinue from study treatment due to reasons other than disease progression will be followed for disease evaluation approximately every 12 weeks or 24 weeks from the latest date of disease evaluation before study treatment discontinuation until disease progression, regardless of whether the subject receives a new anti-CLL therapy.

Survival Follow up: All subjects who have disease progression and have not withdrawn consent will be contacted approximately every 24 weeks by clinical visit or telephone, to assess survival and the use of alternative anti-CLL therapy and occurrence of any secondary malignancies 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, e.g., by repeat telephone calls, certified letter to the subject's last known mailing address, or local equivalent methods. If a public 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 is unsuccessful (or no clear status can be obtained), list subject's status as "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, including those subjects who have withdrawn consent or are classified as "lost to follow-up."
  - Subjects who have withdrawn consent: 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.)
  - Subjects classified as lost to follow-up: Site personnel should check hospital records, the subject's 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.)

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.

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

If 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, the sponsor will not be obliged to destroy the results of this research.

Such subjects will always be asked about the reason(s) and the presence of any AEs. The investigator will follow up subjects as medically indicated. The subject will return electronic ePRO device(s).

The sponsor or its delegate will request investigators to collect information on subjects' vital status (dead or alive; date of death when applicable) at the data cut-off for study analyses from publicly available sources, in accordance with local regulations. Knowledge of the vital status at data cut-off for study analyses in all subjects is crucial for the integrity of the study.

See the SoAs (Table 1, Table 2, and Table 3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. Any remaining study treatment(s) should be returned by all subjects.

8 Study Assessments AND PROCEDURES

Study procedures and their timing are summarised in the SoA (Section 1.1). Descriptions of the scheduled evaluations are outlined in the subsections below. Before study entry, throughout the study, and at the follow-up evaluation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and efficacy assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. Such unscheduled assessments will be captured in the protocol-specific database as appropriate.

The investigator will ensure that data are recorded on the eCRFs. A web-based data capture (WBDC) system will be used for data collection and query handling.

The investigator ensures the accuracy and completeness of eCRFs and timeliness of the data recorded, and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will electronically sign the completed eCRFs. A copy of the completed eCRFs 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.

Medical history must be collected and recorded including concurrent medical signs and symptoms, alcohol use and, if a smoker, cigarette use. Disease history, including the date of initial diagnosis, Rai staging within 28 days of first dose with study drug, and history of autoimmune CLL complications and their treatment will also be recorded based upon available documents and subject history.

Procedures conducted as part of the subject's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes, provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy assessments

8.1.1 Tumor assessments

Overall response assessments will be based upon evaluation of physical exams, recording of symptoms, radiologic evaluations, hematologic evaluations, and bone marrow exams per the SoA.

Baseline:

For baseline, a CT scan with contrast (or MRI if CT is contraindicated) is required within 28 days before the first dose of study drug and must include the neck, chest, abdomen, and pelvis and any other disease sites (e.g., brain). Spleen and liver size should be recorded in CT measurement. Additionally, bone marrow aspiration and biopsy are required within 60 days before first dose of study drug. Physical exam (especially lymph node and organomegaly), B-symptoms, blood counts with differential, and other clinical information at baseline should be recorded in the eCRF.

Up to 6 measurable disease sites (only nodal lesions≥1.5 cm in the longest diameter, 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 according to SoA. Investigators will assess response and progression based on clinical/laboratory signs and symptoms. Radiology reports from a CT scan will be used to support the evaluation of complete and partial response.

Subjects who have signs and symptoms of disease progression outside of the scheduled study visits and assessments should be evaluated by the investigator with physical exam and blood counts 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 (samples from local laboratories can be used if central testing is unavailable). With Amendment 5.0, the blood samples for response or disease progression will be tested in local laboratories. 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. Subjects may continue study treatment until progression is confirmed by a serial exam. 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 anti-CLL therapy should be withheld if clinically appropriate in the absence of confirmed progressive disease.

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 and bone marrow sample must be obtained to evaluate minimal residual disease (MRD). 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." 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 an ancillary whole-body PET-CT scan (not required for study) is performed per local standard of care or at investigator discretion, the results of this scan should be captured in the eCRF as an unscheduled visit.

A central imaging service will be used to provide independent radiologic assessments for the purposes of the primary endpoint. All imaging assessments (including unscheduled visit scan) will be sent to the sponsor appointed central reader on an ongoing basis. Assessment of scans by BICR will be triggered only upon investigator-assessed progression for both arms and the BICR confirmation will be reported back to sites. If the BICR does not confirm disease progression, tumor assessments should be continued in line with the schedule of assessments. Since the primary analysis of the study is based on BICR, it is important that study treatment and scheduled imaging assessments continue until progression confirmed by BICR. After the final analysis and per Amendment 5.0, disease progression can be assessed by investigator.

If at the time of primary PFS analysis it is identified that a patient has disease progression by BICR that has not been identified by the investigator, the sponsor will contact the investigator to discuss whether continued treatment with study medication is appropriate.

The investigator must evaluate the response of the subject per IWCLL criteria (see Table 10).

Table 10 Response Assessment Criteria for CLL (modified from Hallek 2018) – IWCLL Criteria

Group	Parameter	CR a	PR b	PD	SD
A	Lymph nodes	None ≥1.5 cm	Decrease ≥50% (from baseline) c	Increase ≥50% from baseline or from response	Change of -49% to +49%
	Liver and/or spleen size d	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 nadir with absolute count ≥ 5×10^9/L	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 CLL	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	Normocellular, no CLL cells, no B-lymphoid nodules	Presence of CLL cells, or of B-lymphoid nodules, or not done	Increase of CLL cells by ≥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 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." 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.

b 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.

c 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).

d 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.

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. The investigator may use their clinical judgment when assigning the overall response with blood lymphocyte count, as necessary.

8.1.2 Minimal Residual Disease

If the subject's physical examination findings, laboratory evaluations, and radiographic evaluations suggest that PR, CR, or CRi has been achieved, a peripheral blood and bone marrow sample to evaluate MRD by flow cytometry 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 and bone marrow sample testing for minimal residual disease (MRD) will be done at timepoints specified in the SOA. If MRD samples are 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. After FA and per Amendment 5.0, MRD tests are not mandatory and will be locally performed per clinical practice.

8.1.3 Clinical laboratory assessments

See Table 11 for the list of clinical 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.

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, pregnancy test, hepatitis serology 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 hospital practice. If screening assessment clinical chemistry and hematology are performed within 5 days prior to the baseline visit (i.e., first dose day), they do not need to be repeated at the baseline visit. All samples will be used up or disposed of after analyses.

Pregnancy tests are required only for women with childbearing potential. A urine or serum pregnancy test is acceptable. Pregnancy tests will be performed at Screening, on Cycle 1 Day 1, and at the safety-follow-up visit, and may be performed more frequently if required by local regulatory authorities

Hematology testing will be evaluated at the central laboratory and will include a complete blood count (CBC) with WBC 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 for response or progression confirmation. After FA and per Amendment 5.0, hematology testing will be performed locally.

β2-microglobulin: peripheral blood samples will be collected and sent to the central laboratory for β2-microglobulin test. After FA and per Amendment 5.0, the testing is not required and will be locally performed per the discretion of investigator.

T/B/NK cell count (i.e., CD3, CD4, CD8, CD19, CD16/56) will be performed at the central laboratory. After FA and per Amendment 5.0, the testing is not required and will be locally performed per the discretion of investigator.

Cytogenetics and FISH Panel: screening peripheral blood will be sent to a central laboratory to be tested for 17p del, 13q del, trisomy 12, 11q del by FISH and stimulated karyotyping, the status of 17p del is mandatory to be tested by central lab during screening period. A blood sample for FISH evaluation will also be drawn at Cycle 7, and when a subject has disease progression (with PD confirmation from BICR, cytogenetic and genetic molecular prognostic molecules and FISH evaluation need to be performed after signing crossover ICF), at the EoT or SFU visits. If these samples are damaged during collection or shipment, they should be redrawn at the next subsequent visit. After FA and per Amendment 5.0, the testing is not required and will be locally performed per the discretion of investigator.

Genetic molecular prognostic molecules: screening peripheral sample will be sent to central laboratory for sequencing of immunoglobulin heavy-chain variable (IGHV) and p53 mutational status. A blood sample will also be drawn when a subject has disease progression (with PD confirmation from BICR, cytogenetic and genetic molecular prognostic molecules and FISH evaluation need to be performed after signing crossover ICF), at the EoT or SFU visits. After FA and per Amendment 5.0, the testing is not required and will be locally performed per the discretion of investigator.

Table 11 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)
Hematology [b]	
White blood cell (WBC) count with differential	Platelet count
Red blood cell (RBC) count	Absolute neutrophil count (ANC)
Hematocrit	Absolute lymphocyte count (ALC)
Hemoglobin	
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)
Other Tests	
T/B/NK Cell Count [b]	Serum immunoglobulin levels
β2-microglobulin [b]	
Cytogenetics and FISH Panel [b, d]	Genetic molecular prognostic molecules [b, e]

a In case a subject shows an AST or ALT ≥3×ULN together with total bilirubin ≥2×ULN please refer to Appendix D 'Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law,' for further instructions.

b These tests will be performed at the central laboratory.

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 every 3 months thereafter. Monitoring every 3 months should continue until 12 months after last dose of study drug(s) for Arm A and Arm C subjects. For Arm B subjects, monthly monitoring should continue until 12 months after last dose of Arm B treatments. (See Table 1, Table 2, and Table 3, and exclusion criteria #8). 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 2and 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 Cytogenetics and FISH Panel include 17p del, 13q del, trisomy 12, 11q del by FISH and stimulated karyotyping.

e Genetic 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.

8.1.5 CCI [redacted]

[redacted]

8.1.5.1 CCI [redacted]

[redacted]

CCI

CCI

[redacted]

8.2 Safety assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1 Clinical safety laboratory assessments

Clinical safety laboratory assessments are included in Table 11 and specified in the SoA for the timing and frequency.

For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.5.

Additional safety 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 CRF.

8.2.2 Physical examination

A physical examination will be performed and include an assessment of the following: 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 examination of palpable lymph nodes and spleen and liver below the costal margin on the respective side. Only physicians 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 medical note. 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 8.3.5 for details.

8.2.3 Vital signs

Body temperature, pulse rate, respiratory rate and blood pressure will be assessed after the subject has rested in the sitting position.

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

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

Single 12-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 in supine position after the subject has been resting for at least 10 minutes. Additional ECG testing could be scheduled as clinically indicated, a standardized ECG machine should be used, and the subject should be examined using the same machine throughout the study if possible.

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 per SoA thereafter according to ECOG criteria as shown in Table 12 .

Table 12 ECOG Performance Status Scale

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, recording, and reporting events that meet the definition of an AE.

8.3.1 Time period and frequency for collecting AE and SAE information

AEs and SAEs will be collected by the site from the time of signature of informed consent form throughout the treatment period and including the follow-up period. After the signing of the ICF and prior to the first dose of study treatment all SAEs, regardless of causality, must be reported to the sponsor. Collection and reporting of AEs and SAEs after the final DCO is described in Section 8.3.11.

All AEs and SAEs will be reported from first dose of study treatment 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 that are believed to be related to the study treatment or any AEs of concern (deemed by the sponsor or investigator), regardless of causality to the study treatment as relevant.

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.

Table 13 Guidance for Reporting Adverse Events

	AEs	SAEs	AESIs	AEs of concern
Signing of ICF – First dose of study treatment	Not reported (recorded as medical history)	Related (to study procedure) Unrelated	Not reported (recorded as medical history)	Not reported (recorded as medical history)
First dose of study treatment – 30 days after last dose of study treatment	Related Unrelated	Related Unrelated	Related Unrelated	Related Unrelated
Post-30 days after last dose of study treatment	Not reported	Related	Not reported	Related Unrelated

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 data in former study subjects. However, if at any time after a subject's last visit the investigator learns of any SAE, including a death, that is considered to be reasonably related to the study treatment or study participation, the investigator may notify the sponsor.

8.3.2 Follow-up of AEs and SAEs

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 eCRF. The sponsor 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.

Adverse event variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- CTCAE grade/max CTCAE grade/changes in CTCAE grade
- Whether the AE is serious or not (Appendix B).
- Investigator causality rating against the IP(s) (yes or no)
- Action taken with regard to IP(s)
- AE caused participant's withdrawal from study (yes or no).
- Administration of treatment for the AE.
- Outcome

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

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- Seriousness criteria
- Date of hospitalisation
- 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

The grading scales found in the National Cancer Institute CTCAE will be utilised 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).

8.3.3 Causality collection

The investigator should assess causal relationship between Investigational Product and each Adverse Event, 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 investigational product?'*

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

A guide to the interpretation of the causality question is found in Appendix B.

8.3.4 AEs based on signs and symptoms

All AEs spontaneously reported by a 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 eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) over 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.

8.3.5 AEs based on examinations and tests

The results from the Clinical Study Protocol-mandated laboratory tests,vital signs physical examinations, and ECGs will be summarised in the clinical study report (CSR).

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, ECG, or other safety assessment should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the IP or are considered to be clinically relevant as judged by the investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study treatment, e.g., dose adjustment or drug interruption).

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/ECG or other safety assessment will be considered as additional information. Wherever possible, the reporting investigator should use clinical rather than laboratory terms (e.g., 'anaemia' versus 'low haemoglobin 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 that 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 under study.

8.3.6 Hy's law

Cases where a subject shows elevation in liver biochemistry may require further evaluation, and occurrences of AST or ALT $\geq$3×ULN, together with total bilirubin $\geq$2×ULN, 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.

8.3.7 Disease progression

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the IP is being studied. It may be an increase in the severity of the disease under study and/or increases 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 that are unequivocally due to disease progression should not be reported as AEs during the study.**

Hospitalization due solely to the progression of underlying malignancy should NOT be reported as an SAE. Clinical symptoms of progression may be reported as AEs if the symptoms cannot be determined as exclusively due to the progression of the underlying malignancy, or if they do not fit the expected pattern of progression for the disease under study.

Symptomatic deterioration may occur in some subjects. Symptomatic deterioration is when progression is evident in the subject's clinical symptoms and the investigator may elect not to perform further disease assessments. If there is any uncertainty about an AE being due only to the disease under study, it should be reported as an AE or SAE.

8.3.8 Second primary malignancies

AEs for malignant tumors reported during a study should generally be assessed as SAEs. If no other seriousness criteria apply, the "Important Medical Event" criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a nonserious AE. For example, if the tumor is included as medical history and progression occurs during the study but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as nonserious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumor event in question is a new malignant tumor (i.e., it is not the tumor for which entry into the study is a criterion and that is being treated by the investigational product under study and is not the development of new or progression of existing metastasis to the tumor under study). Malignant tumors that—as part of normal, if rare, progression—undergo transformation (e.g., Richter's transformation of B-

cell chronic lymphocytic leukemia into diffuse large B-cell lymphoma) should not be considered a new malignant tumor.

8.3.9 Deaths

All deaths that occur during the study, or within the follow-up period after the administration of the last dose of IP, must 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. It should also be documented in the Statement of Death page in the eCRF. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign the main and contributory causes of death.
  - Death with an unknown cause should always be reported as an SAE and documented in the Statement of Death page in the eCRF, but every effort should be made to determine 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 a sponsor representative within the usual timeframes.

Deaths occurring after the protocol-defined follow-up period after the administration of the last dose of study intervention should be documented in the Statement of 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 intervention, then it should also be reported as an SAE.

8.3.10 Adverse Event of Special Interest (AESI)

AESIs are events of scientific and medical interest specific to the further understanding of the investigational product safety profile and require close monitoring and rapid communication by the investigator to the sponsor.

The following events are AESIs for subjects receiving acalabrutinib treatment arm and must be reported to the sponsors expeditiously, irrespective of regulatory seriousness criteria or causality:

- Ventricular arrhythmias (e.g., ventricular extrasystoles, ventricular tachycardia, ventricular arrhythmia, ventricular fibrillation, etc.)

8.3.11 Safety Data to be Collected Following the Final Data Cutoff of the Study

For participants continuing to receive acalabrutinib after the final DCO, AEs and SAEs will be collected, but only SAEs will be reported. In addition, 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). All data after the final DCO and database closure will be recorded in the participant notes but, with the exception of SAEs, will not otherwise be reported for the purposes of this study.

All SAEs that occur in participants still receiving acalabrutinib after the final DCO must be reported as detailed in Section 8.4.1.

8.4 Safety reporting and medical management

8.4.1 Reporting of SAEs

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

If any SAEs occur in the course of the study, then investigators or other site personnel should inform the appropriate sponsor representatives within 1 day, i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

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

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

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 sponsor representative.

If the EDC system is not available, then the investigator or other study site staff reports an SAE to the appropriate sponsor representative by submitting a paper SAE report as back-up.

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

8.4.2 Pregnancy

All pregnancies and outcomes of pregnancy with conception dates following the first date of study intervention, including pregnancy in the partner of male participants, should be reported to the sponsor.

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, the IP should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP 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 in a subject during exposure to investigational product and until 2 days after the last dose of acalabrutinib or 12 months after the last dose of rituximab or chlorambucil, whichever is longer, then the investigator or other site personnel informs the appropriate sponsor representatives within 1 day, i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated sponsor representative works with the investigator to ensure that all relevant information is provided to the sponsor 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 eCRF-PREGREP module is used to report a pregnancy; the eCRF-PREGOUT module is used to report the outcome of a pregnancy.

8.4.2.2 Paternal exposure

Non-sterilised male subjects who intend to be sexually active with a female partner of childbearing potential should refrain from fathering a child or sperm donation for the duration

of the study (from the time of screening) and for 90 days after the last dose of rituximab or chlorambucil, whichever is later.

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 anomaly) occurring from the date of the first dose of study intervention until 2 days after the last dose of acalabrutinib or 90 days after the last dose of rituximab or chlorambucil, whichever is longer, 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.

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

If an overdose on a acalabrutinib occurs in the course of the study, then the investigator or other site personnel inform appropriate sponsor representatives immediately, or **no later than 24 hours** of when he or she becomes aware of the overdose.

The designated sponsor representative works with the investigator to ensure that all relevant information is provided to the sponsor Patient Safety data entry site within 1 or 5 calendar days for overdoses associated with a SAE (see Section 8.4.1) and within 30 days for all other overdoses.

For participants receiving SoC (rituximab and chlorambucil), refer to the local Prescribing Information for treatment of cases of overdose. If any overdose is associated with an AE or SAE, the AE/SAE diagnosis or symptoms are recorded in the relevant AE modules and SAEs are reported to the sponsor Patient Safety data entry site for entry into the safety database (see Section 8.4.1).

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 8.4.1) and **within 30 days** for all other events.

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 (NIMP) that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition and examples of medication error can be found in Appendix 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 Dose modification management of IP-related toxicities

Dose modification management of IP-related toxicities can be found in Section 6.6.

8.5 Pharmacokinetics

Sparse PK samples will be collected from all subjects randomized to Arm A, to investigate the pharmacokinetics of acalabrutinib and ACP-5862 (acalabrutinib's metabolite). Blood samples for PK will be collected from each Arm A subject according to the timepoints shown in Table 14.

Table 14 Arm A PK Sampling Schedule

Visit	Time Point	Sample Type and Analyte
Cycle 2 Day 1	Predose (within 30 minutes before dosing)	Plasma for acalabrutinib Plasma for ACP-5862
	1 hour (±15 minutes) after dosing	Plasma for acalabrutinib Plasma for ACP-5862
	2 hours (±15 minutes) after dosing	Plasma for acalabrutinib Plasma for ACP-5862
	4 hours (±30 minutes) after dosing	Plasma for acalabrutinib Plasma for ACP-5862

On the day of sampling, the subject will not take a dose of any study drug before arrival at the clinic. The subject will bring a meal (preferably the first meal of the day) to the clinic, and the morning dose of acalabrutinib will be taken within 30 minutes after eating the meal. The study drug administration will be observed by clinic staff. The actual time of the observed dose and the blood draws for PK samples must be accurately recorded, to the minute, in the eCRF. PK samples must be processed according to the instructions in the lab manual.

At each time point, PK samples should be collected and processed according to the instructions in the laboratory manual. Samples will be shipped to a central laboratory. The central laboratory will ship the samples to the bioanalytical laboratory as directed.

Drug concentration information that may unblind the study will not be reported to blinded personnel until the study has been unblinded.

8.5.1 Determination of drug concentration

Samples for determination of acalabrutinib and ACP-5862 concentrations in plasma will be analysed by analytical test sites on behalf of the sponsor, using validated bioanalytical methods. Full details of the analytical method used will be described in a separate bioanalytical report.

8.5.2 Storage and destruction of pharmacokinetic samples

PK samples will be stored and disposed of according to local laws and regulations. The residual PK samples will be disposed of after the CSR finalization.

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 / medical resource utilization and health economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9 Statistical CONSIDERATIONS

9.1 Statistical hypotheses

The primary objective of the study is to test the following hypothesis:

H0: BICR-assessed PFS of Arm A is the same as Arm B

H1: BICR-assessed PFS of Arm A is not the same as Arm B

The study will be considered positive (a success) if the primary PFS analysis result for Arm A versus Arm B is statistically significant.

9.2 Sample size determination

Under the exponential model assumptions, this study is expected to randomize approximately 75 patients per arm (150 patients in total from both arms) with 1:1 randomization ratio. It is planned to randomize approximately 75 to 120 patients in total from both arms (50% to 80% of total sample size) from China. The study is sized to achieve more than 95% power to detect a hazard ratio of 0.333 in PFS (which translates into an improvement in median PFS from 30 months to 90 months) at the 2-sided significance level of 0.05, allowing for one interim analysis conducted at approximately 76% of the target events. The sample size calculation assumes a median PFS of 30 months in Arm B (Michallet et al 2018).

The final analysis of BICR-assessed PFS is event-driven and will be conducted when enrollment is completed and there are approximately 50 BICR-assessed PFS events in total from Arm A and Arm B. The accrual period is assumed to be approximately 30 months. It is assumed that about 5% of the patients in each arm will drop out at the time of final PFS

analysis. The interim and final analysis are anticipated to occur approximately 40 months and 53 months, respectively, after the first patient is randomized.

One interim analysis will be conducted to assess early efficacy of Arm A versus Arm B with respect to the primary efficacy endpoint, BICR-assessed PFS using Lan and DeMets spending function with O'Brien-Fleming boundary (Lan and DeMets 1983; O'Brien and Fleming 1979). The interim analysis will occur when approximately 38 BICR-assessed PFS events (76% of target PFS events required for final analysis) have been observed in both arms combined. The nominal alpha level for the interim and final analysis of 38 and 50 BICR-assessed PFS events is 0.02 and 0.044 respectively. The actual nominal alpha level will be determined based on the number of BICR-assessed PFS events observed at the time of each respective analysis.

EAST 6.5 was employed to conduct the sample size calculation.

9.3 Populations for analyses

Populations of the full analysis set, safety analysis set, and PK analysis set are defined in Table 15. The population sets and corresponding outcome variables are shown in Table 16.

Table 15 Analysis Populations

Population	Description
Full analysis set	All randomized patients (ITT population)
Safety analysis set	All subjects who have received at least 1 dose of investigational product. Erroneously treated subjects (e.g., those randomised to Arm A but actually given Arm B treatment) are accounted for in the treatment group of the treatment they actually received.
PK analysis set	All randomized patients that have at least 1 post-dose evaluable concentration-time data for PK analysis.

Table 16 Analysis Sets for Outcome Variables

Outcome variable	Population
Efficacy Data (BICR- and INV-assessed)	
PFS	Full analysis set (ITT population)
ORR, DOR, TTNT, OS, MRD rate, CCI	
Demography	
Safety Data	
Exposure	Safety analysis set
AEs	
Laboratory measurements	

Table 16 Analysis Sets for Outcome Variables

Outcome variable	Population
Vital signs	
ECGs	
PK Data	PK analysis set

9.4 Outcome measures for analyses

9.4.1 Calculation or derivation of efficacy variables

9.4.1.1 Progression-free survival

PFS is defined as the time from the date of randomization until progression (assessed by the BICR per IWCLL 2018 criteria) or death from any cause, whichever occurs first. 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. For subjects without an adequate post-baseline disease assessment, PFS will be censored on the date of randomization unless they die within 2 visits of baseline.

PFS will also be obtained using the same derivation rule described above based on investigator assessment.

9.4.1.2 Overall response rate

ORR is defined as the proportion of patients who have a CR, CRi, nPR or PR assessed by BICR per IWCLL 2018 criteria at or before initiation of subsequent anticancer therapy. CRi 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. 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 randomization date, but prior to starting any subsequent anticancer therapy, up to and including progression or the last evaluable assessment in the absence of progression.

ORR and BOR will also be obtained using the same derivation rule described above based on investigator assessment.

9.4.1.3 Duration of response

DOR (assessed by BICR per IWCLL 2018 criteria) is defined as the time from the date of first documented response until date of documented progression or death in the absence of disease progression. 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.

DOR will also be obtained using the same derivation rule described above based on investigator assessment.

9.4.1.4 Time to next therapy

Time to next therapy (TTNT) is defined as time from randomization until 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 the statistical analysis plan (SAP).

9.4.1.5 Overall survival

Overall survival is the length of time from randomization until the date of death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.

9.4.1.6 Minimum residual disease rate

MRD negative rate is defined as the proportion of subjects with MRD-negativity (defined as <1 CLL cell per 10,000 leukocytes).

9.4.2 Calculation or derivation of safety variables

Safety and tolerability will be assessed in terms of AEs (including SAEs), laboratory data, vital signs, ECGs, and exposure. These will be collected for all subjects. 'On treatment' will be defined as assessments between date of first dose and 30 days following discontinuation. Appropriate summaries of these data will be presented as described in Section 9.5.2.

9.4.2.1 Other significant adverse events

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

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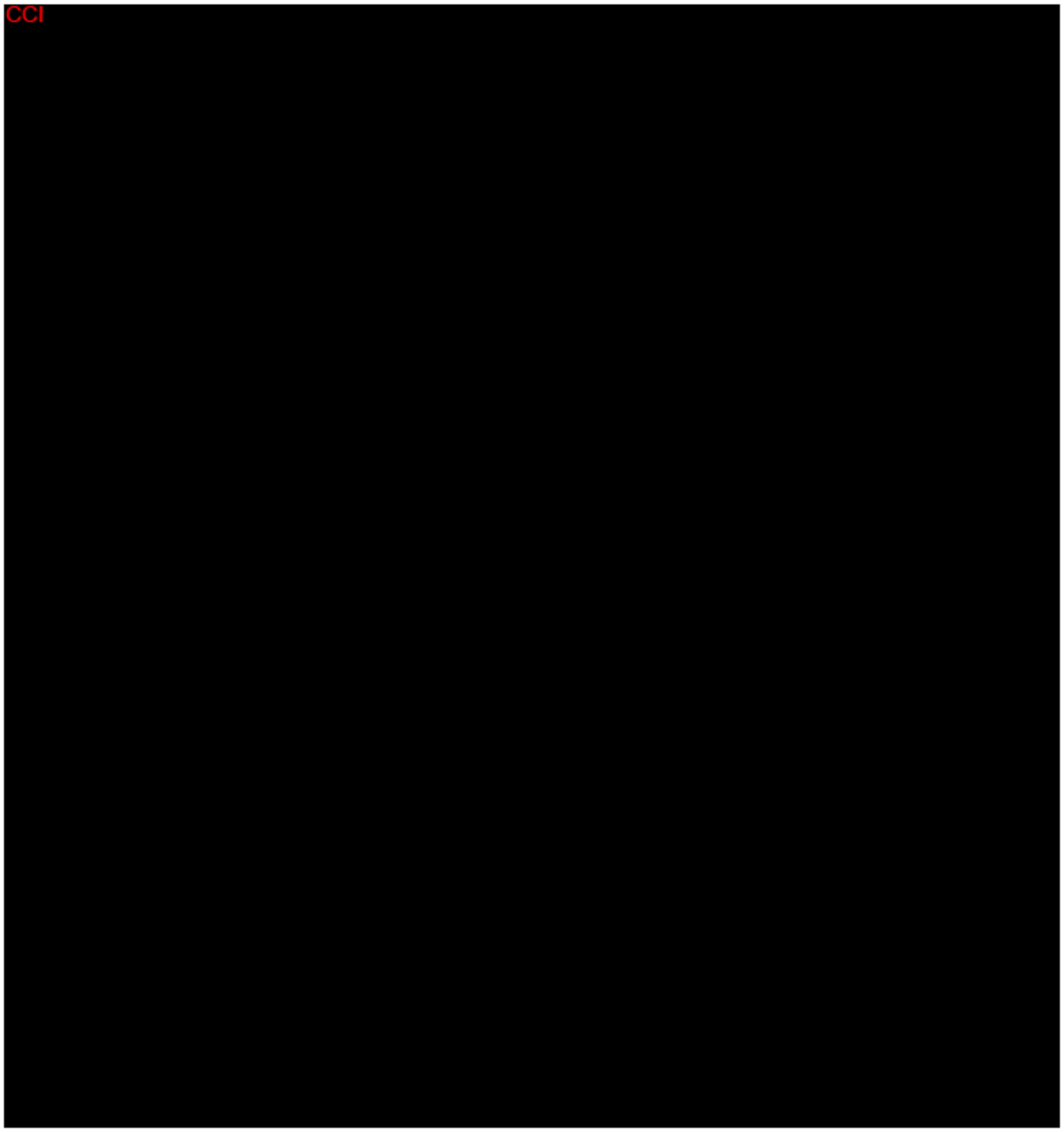

9.5 Statistical analyses

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

Descriptive statistics will be used for all variables, as appropriate, and will be presented by treatment group. Unless otherwise stated, continuous variables will be summarized by the

number of observations, mean, standard deviation, median, minimum, and maximum; categorical variables will be summarized by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the population total for the corresponding treatment arm.

In general, the baseline value for statistical analysis is the last non-missing value prior to administration of the first dose of IP, except for efficacy variables. For efficacy variables, baseline is defined as the last assessment prior to randomization.

All data collected will be listed. Efficacy and CCI data will be summarized and analyzed based on the FAS. Safety data will be summarized on the safety analysis set. PK data will be summarized on the PK analysis set.

The efficacy and safety in China subgroup may be analyzed to facilitate a benefit-risk assessment for regulatory submission in China. Details of this analysis will be specified in the SAP.

9.5.1 Efficacy analyses

9.5.1.1 Progression-free survival

The primary analysis will be performed in the ITT population to compare PFS as assessed by the BICR using a 2-sided stratified log rank test, adjusting for ECOG (0-1 versus 2) and Rai stage (Stage 0-II versus III-IV) at randomization. The estimate of the HR and its corresponding 95% CI will be computed using a Cox proportional hazards model stratified by the randomization strata.

Kaplan-Meier plots of PFS will be presented by treatment arm. Summaries of the number and percentage of patients experiencing a PFS event and the type of event (progression or death) will be provided along with median PFS for each treatment.

The following sensitivity analyses will be performed:

- Unstratified log rank test and unstratified Cox model.
- Ascertainment bias will be assessed by analyzing investigator data. The stratified log-rank test used for the primary PFS analysis will be repeated.
- One sensitivity analysis will be performed by repeating the primary analysis, except that actual PFS event times after subsequent therapy will be used rather than censored times.

Subgroup analyses will be conducted comparing PFS between Arm A versus Arm B in the following subgroups (but not limited to):

- Age at randomization (<65 versus ≥65)
- Sex (male versus female)

- ECOG (0-1 versus 2)
- IGHV mutation status (mutated versus non-mutated)
- Country (China versus other)
- Rai stage at screening (Stage 0-II versus III-IV)
- β2-microglobulin at baseline (≤3.5 mg/L versus >3.5 mg/L)
- Bulky disease (longest diameter of lymph node <5 cm versus ≥5 cm at baseline)

The HR and corresponding 95% CI for each subgroup will be calculated based on an unstratified Cox regression model and presented in a forest plot as appropriate.

Other baseline variables may also be assessed if there is clinical justification or an imbalance is observed between the treatment groups. The purpose of the subgroup analyses is to assess the consistency of treatment effect across expected prognostic and/or predictive factors.

Unless there is a marked difference between the results of the statistical analyses of the PFS from the BICR data and that of the site investigator tumor data, these subgroup analyses will only be performed on the PFS endpoint using the BICR data.

No adjustment to the significance level for testing of the subgroup and sensitivity analyses will be made since all these analyses will be considered supportive of the analysis of PFS.

Further details will be provided in the SAP.

9.5.1.2 Overall response rate

ORR (assessed by BICR per IWCLL 2018 criteria) will be compared between treatment arms (Arm A versus Arm B) using the Cochran-Mantel-Haenszel (CMH) chi-square test, adjusted for randomization stratification factors.

Number and percentage of patients with a tumor response (CR, CRi, nPR, or PR) will be presented by treatment arm. For each treatment arm, best overall response (BOR) will be summarized by n (%) of each category (CR, CRi, nPR, PR, SD, PD, NE). No formal statistical analysis is planned for BOR.

ORR and BOR assessed by investigator will be analyzed in the same fashion as that for BICR-assessed ORR and BOR.

9.5.1.3 Duration of response

DoR assessed by BICR or investigator per IWCLL 2018 criteria will be analyzed in the same fashion as that for primary efficacy endpoint PFS as described in Section 9.5.1.1.

9.5.1.4 Time to next therapy

TTNT will be analysed in the same fashion as that for primary efficacy endpoint PFS as described in Section 9.5.1.1.

9.5.1.5 Overall survival

OS will be analysed in the same fashion as that for primary efficacy endpoint PFS as described in Section 9.5.1.1.

A sensitivity analysis will be performed. Patients who receive crossover therapy will be censored at the date before first dose date of the crossover therapy.

9.5.1.6 MRD negativity rate

Peripheral blood MRD negativity rate at the start of Cycle 9 will be compared between treatment arms (Arm A versus Arm B) using the CMH chi-square test, adjusted for randomization stratification factors.

9.5.2 Safety analyses

Safety analyses will be performed using the safety analysis set. Unless noted elsewise, summaries will be based on safety data collected in the initial treatment period (i.e., for patients who cross over to Arm A, the safety data on or after receiving first dose of cross-over therapy will be excluded). Safety data on or after receiving first dose of cross-over therapy might be summarized separately, provided that there are a sufficient number of patients to warrant this.

All safety data will be listed.

Adverse Events

Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) that will have been released for execution at the sponsor/designee.

Safety data will be presented using descriptive statistics unless otherwise specified.

AEs will be presented for each treatment group by SOC and/or PT covering number and percentage of subjects reporting at least one event and number of events where appropriate.

AEs occurring prior to start of IP, treatment emergent AEs, and post-treatment AEs will be presented separately.

An overview of AEs will be presented for each treatment group the number and percentage of subjects with any AE, AEs with outcome of death, serious AEs, and AEs leading to discontinuation of IP, as well as AEs leading to IP dose delays, AEs leading to IP dose reduction as well as the number of individual occurrences in those categories.

Separate AE tables will be provided taken into consideration relationship as assessed by the investigator, CTCAE grading, seriousness, death and events leading to discontinuation of IP as well as other action taken related to IP, events of special interest, Other significant adverse events.

An additional table will present number and percentage of subjects with most common AEs (frequency of >5%).

Key subject information will be presented for subjects with AEs with outcome of death, serious AEs, and AEs leading to discontinuation of IP.

An AE listing for the safety analysis set will cover details for each individual AE.

Full details of AE analyses will be provided in the SAP.

Treatment Emergent

The following events are considered treatment emergent:

- Adverse events with an onset date on or after first dose of IP, and within 30 days after last dose of IP
- Worsening of pre-existing events on or after first dose of IP, and within 30 days after last dose of IP

Clinical Laboratory Tests

Data Summary Methods

For gradable parameters, a summary of worst post-baseline toxicity grade will be provided in the "on-treatment" period by treatment arm. Appropriate summaries of laboratory data over time and change from baseline will be provided by treatment arm.

Analysis of Lymphocytosis

For all subjects with baseline and any post-baseline ALC measurements, ALC at peak summary will be provided by treatment arm.

Lymphocytosis is defined as an ALC >5000 cells/µL and an increase above baseline. The number of subjects with at least one occurrence of lymphocytosis will be summarized. For subjects with lymphocytosis, resolution of lymphocytosis is defined as 1) a decrease of ALC value to the baseline level or lower, or 2) an achievement of ALC value that is below 5,000 cells/µL, whichever occurs first. The following analyses will be conducted for subjects with lymphocytosis by treatment arm: ALC at peak and time to peak ALC for subjects who have lymphocytosis. The data will be summarized by descriptive statistics.

Duration of lymphocytosis is defined as the duration of time from the earliest date on which the ALC value met the lymphocytosis criteria at a post-baseline assessment to the earliest date on which a subsequent ALC value met the resolution criteria.

Analysis of Serum Immunoglobulins

Serum immunoglobulins (IgA, IgG, and IgM) are collected as scheduled in the SoA. For each variable, descriptive statistics will be presented at each scheduled post-baseline assessment by treatment arm. Subjects who received IVIG on the study will be excluded from the summary for IgG.

ECOG Performance Status

The ECOG performance status will be collected as scheduled in the SoA. The ECOG performance status grade ranges from 0–5. Descriptive statistics and change from baseline will be provided for each visit over time.

Weight

Descriptive statistics and change from baseline will be provided over time.

Vital signs

Vital sign parameters will be presented for each treatment group. Summary statistics for continuous variables cover n, mean, SD, Min, Q1, median, Q3, and Max. Frequency tables cover number and percentage of subjects in the respective category.

For each scheduled post-baseline visit, descriptive statistics for all vital sign parameters will be presented for observed values and change from baseline.

Details of vital signs analyses will be provided in the SAP.

9.5.3 CCI [redacted]

[redacted]

9.5.4 PK analyses

Plasma concentrations of acalabrutinib and ACP-5862 will be tabulated for each subject in Arm A by visit and time point. Summary statistics (including but not limited to: geometric mean, coefficient of variation, geometric mean ± geometric standard derivation, arithmetic mean, standard derivation, minimum, median, maximum, and number of observations) will be presented as appropriate.

9.5.5 Other analyses

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

9.5.6 Methods for multiplicity control

To control the overall type I error at 0.05 level, the Lan-Demets alpha spending function based on the O'Brien-Fleming boundary is used to split alpha for the interim and final analyses of PFS. If exactly 76% of PFS events at final is available at the time of the interim analysis, that is 38/50 PFS events based on BICR have occurred, the 2-sided alpha level to be applied for the interim and the final analysis will be 0.02 and 0.044, respectively. The nominal alpha levels for the interim and final analyses will be determined based on actual number of PFS events observed at the time of the analyses.

9.6 Interim analyses

This protocol includes one interim analysis and a final analysis. The Statistical Analysis Plan will describe the planned interim analyses in greater detail.

The interim analysis will be performed to test for superiority of Arm A relative to Arm B. This analysis will be performed when approximately 38 PFS events based on BICR have been observed in the study (25.3% maturity or 76% information fraction). It is assumed that about 5% of the patients in each arm will drop out at the time of final PFS analysis. The interim analysis is anticipated to occur approximately 40 months after the first patient is randomized.

9.6.1 Data monitoring committee

An independent data monitoring committee (IDMC) will be utilized for this study. Appendix A 5 provides more details on the rationale for and the remit of the committee.

The IDMC will evaluate efficacy for the interim analysis. Additional IDMC safety review will be conducted with first safety data review will be performed by the IDMC after approximately 50 subjects have been randomized. Thereafter, the IDMC will meet approximately every 6 months or at a frequency determined by the IDMC and the sponsor according to the emerging safety profile. Members of the IDMC will be external to the sponsor. An IDMC charter will

be developed which will specify the Committee's responsibilities, authorities, and procedures along with details of the analysis planning, decision-making guidance, and dissemination of the results as well as the recommendations and decisions after the analysis.

Full details of the IDMC procedures, processes, safety review and interim analysis can be found in the IDMC charter.

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