PROTOCOL

TITLE:	An Open-label, Phase 1b/2 Study of Acalabrutinib Alone or in Combination Therapy in Subjects with B-cell Non-Hodgkin Lymphoma
PROTOCOL NUMBER:	ACE-LY-003
STUDY DRUG:	Acalabrutinib (ACP-196)
IND NUMBER:	118717
EU CT NUMBER	2023-508141-40-00
SPONSOR MEDICAL MONITOR	Medical Monitor name and contact information will be provided separately
SPONSOR:	Acerta Pharma BV Kloosterstraat 9 5349 AB Oss The Netherlands
PROTOCOL DATE:	Version 0.0 - 02 June 2014
AMENDMENT 1 DATE:	Version 1.0 - 20 February 2015
AMENDMENT 2 DATE:	Version 2.0 – 08 May 2015
AMENDMENT 3 DATE:	Version 3.0 – 18 March 2016
AMENDMENT 4 DATE	Version 4.0 – 23 Aug 2017
AMENDMENT 5 DATE	Version 5.0 – 05 Jul 2018
AMENDMENT 6 DATE	Version 6.0 – 05 March 2020
AMENDMENT 7 DATE	Version 7.0 – 14 July 2022
AMENDMENT 8 DATE	Version 8.0 – 12 October 2023 (all sites global consolidation version for EU-CTR)

PROTOCOL APPROVAL PAGE VERSION 8.0

I have carefully read Protocol ACE-LY-003 entitled “An Open-label, Phase 1b/2 Study of Acalabrutinib Alone or in Combination Therapy in Subjects with B-cell Non-Hodgkin Lymphoma”. I agree to conduct this study as outlined herein and in compliance with Good Clinical Practices (GCP) and all applicable regulatory requirements. Furthermore, I understand that the Sponsor and the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) must approve any changes to the protocol in writing before implementation.

I agree not to divulge to anyone, either during or after the termination of the study, any confidential information acquired regarding the investigational product and processes or methods of the Sponsor. All data pertaining to this study will be provided to the Sponsor. The policy of the Sponsor requires that any presentation or publication of study data by clinical investigators be reviewed by the Sponsor, before release, as specified in the protocol.

Principal Investigator’s Signature Date

Print Name

SUMMARY OF AMENDMENT 8.0

This protocol was amended to include details of a new acalabrutinib formulation (acalabrutinib maleate tablet), as approved under NDA 216387. Acalabrutinib maleate tablets and acalabrutinib capsules are bioequivalent, and patients may be switched between the original capsule formulation and the updated tablet formulation at the earliest convenience.

In addition, the protocol has been updated to prepare for the transition to EU-CTR.

Clarifying edits and typographical changes have been made throughout the protocol. The following changes were made as part of this amendment:

Sections Impacted	Rationale	Substantial / Non-substantial
PROTOCOL TITLE PAGE	Added EU CT number and Sponsor address.	Non-substantial
STUDY SYNOPSIS	Updated to reflect changes in the body of the protocol	Substantial
Sections 1.2.1, 1.3.2, 3.4.1, 3.4.2, 3.4.3, 3.4.4, 3.4.5, 3.4.6, 3.5.2, 3.5.3, and 3.5.4.	Added text/ information relating to acalabrutinib tablets.	Substantial
Section 3.2	Clarified definition of the end of study according to EU and FDA requirements. For consistency and alignment in terms of posting study results and to comply with EU CTR.	Substantial
Section 3.7.1	Updates to describe potential risk of hepatotoxicity to align with the current IB.	Substantial
Section 3.7.3	Updates to risk associated with lenalidomide	Substantial
Section 3.7.4	Updated text relating to dietary restrictions.	Substantial
Sections 3.6.3 and 3.7.5	Amended the text on agents that reduce gastric acid so that the restrictions are specific to acalabrutinib capsules.	Substantial
Section 3.7.7	Added description of reporting of overdose. Update required to comply with EU CTR.	Substantial
Section 6.3.1	Clarified the adverse event reporting period.	Substantial
Section 6.3.7	Added description of Medication Error, Drug Abuse and Drug Misuse definition and examples. Update required to comply with EU CTR.	Substantial
Section 7.1	Added sub-section on regulatory reporting requirements for SAEs to comply with regulatory requirements (EU CTR) and global company requirement.	Substantial

Section 7.1	Added sub-section on Serious Breaches. Update required to comply with regulatory requirements (EU CTR) and global company requirement.	Substantial
Section 7.2	Updated section on IRB/IEC to reflect current study status.	Non-substantial
Section 7.5	Updated text relating to study monitoring requirements and audits and inspections to comply with EU CTR.	Substantial
Section 7.6	Updated section describing quality control and quality assurance to comply with EU CTR.	Substantial
Section 7.7	New section added describing data handling and recordkeeping to comply with EU CTR.	Substantial
Section 7.7	Updated information about retention timelines of records and documents to 25 years after study archiving or as required by local regulations. Update required to comply with EU-CTR.	Substantial
Section 7.11	Section updated describing investigational study drug accountability to comply with EU CTR.	Substantial
Appendix 3	Added Seville oranges and starfruit as strong inhibitors of CYP3A.	Substantial
Appendix 9	Added description of Medication Error, Drug Abuse and Drug Misuse definition and examples. Update required to comply with EU CTR.	Substantial
Appendix 10	Added information on Data Quality Assurance. Update required to comply with EU CTR	Substantial
Appendix 11	Updated information about timelines for submission of trial results summaries to EU CTIS. Update required to comply with EU CTR.	Substantial
Appendix 12	Added a summary of country specific changes made to the local CSPs. Update required to comply with EU CTR.	Substantial
Throughout Minor editorial, formatting, and typographical updates and corrections have been made.	Minor corrections made for document clarity	Non-substantial

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In–Text Tables

In-Text Figures

Appendices

Abbreviations

Abbreviation	Definition
λ_z	terminal elimination rate constant
5PS	5-point scale
ABC	activated B-cell like
ACP-196	acalabrutinib
ACP-5862	acalabrutinib's active metabolite (M27)
AE(s)	adverse event(s)
AESI	adverse event of special interest
ALT	alanine aminotransferase
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{0-12}	area under the plasma concentration-time curve from 0 to 12 hours, calculated using linear trapezoidal summation.
$AUC_{0-24calc}$	area under the plasma concentration-time curve from 0 to 24 hours, calculated by doubling the value for AUC_{0-12}
$AUC_{0-\infty}$	area under the plasma concentration-time curve from 0 to infinity, calculated using the formula: $AUC_{0-\infty} = AUC_{0-t} + C_t / \lambda_z$, where λ_z is the apparent terminal elimination rate constant
AUC_{0-t}	area under the plasma concentration-time curve calculated using linear trapezoidal summation from time 0 to time t, where t is the time of the last measurable concentration (Ct)
AUC_{inf}	area under the plasma concentration-time curve from 0 to infinity
BCR	B-cell receptor
BID	twice per day (dosing)
BRCP	breast cancer resistance protein
BTK	Bruton tyrosine kinase
BTK-TO	Bruton tyrosine kinase target occupancy
CD	cluster of differentiation
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practices
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CL/F	oral clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed plasma concentration

CR	complete remission (response)
CSP	Clinical study protocol
CSR	Clinical Study Report
CSSF	Clinical Supplies Shipping Receipt Form
C_t	time of last measurable concentration
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CTIS	Clinical Trial Information System
CTR	Clinical Trials Regulation
CTT	Clinical Trial Transparency
CYP	cytochrome P450
DES	Data Entry Site
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
DVT	deep vein thrombosis
EC_{50}	half-maximal response effective concentration
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FDG	[18F]fluorodeoxyglucose
FIH	first-in-human (trial)
FL	follicular lymphoma
FSH	follicle-stimulating hormone
GCB	germinal center B-cell like
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GLP	Good Laboratory Practices
GRAD	Global Retention and Disposal

HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDT/ASCT	high-dose chemotherapy with autologous stem cell transplantation
IC_{50}	inhibitory concentration 50%
ICF	informed consent form
IEC	Independent Ethics Committee
Ig	immunoglobulin
IHC	immunohistochemistry
IMP	Investigational medicinal product
IRB	Institutional Review Board
IV	intravenous
IVIG	intravenous immunoglobulins
LDi	longest transverse diameter of a lesion
LTFU	long-term follow-up
MALT	mucosa-associated lymphoid tissue
MCL	mantle cell lymphoma
MDS	myelodysplastic syndrome
MRD	minimal residual disease
MRI	magnetic resonance imaging
MZL	marginal zone lymphoma
NHL	non-Hodgkin lymphoma
NIMP	Non-investigational medicinal product
NK	natural killer (cells)
NOAEL	no observed adverse effect level
NFkB	nuclear factor kappa beta
ORR	overall response rate
OS	overall survival
PBMC(s)	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PD	pharmacodynamic
PET	positron-emission topography
PFS	progression-free survival
PI3K	phosphoinositide-3 kinase
PK	pharmacokinetic

PMBCL	primary mediastinal large B-cell lymphoma
PML	progressive multifocal leukoencephalopathy
PO	per os (mouth)
PPD	cross product of the LDi and perpendicular diameter
PR	partial remission (response)
PTAP	Post Trial Access Program
QD	once per day (dosing)
QTc	corrected QT interval
QTcF	corrected QT interval using Fridericia formula
R-CHOP	Rituximab-CHOP
R-DHAP	rituximab, cisplatin, cytarabine, and dexamethasone
REMS	Risk Evaluation and Mitigation Strategy
R-ICE	rituximab, ifosfamide, carboplatin, and etoposide
R/R	relapsed or refractory
SAE(s)	serious adverse event(s)
SAP	Statistical Analysis Plan
SDi	shortest axis perpendicular to the LDi
SFU	safety follow-up
SPD	sum of the product of the diameters
SUSAR	Suspected Unexpected Serious Adverse Reaction (report)
SYK	spleen tyrosine kinase
$t_{½}$	terminal elimination half-life
TLS	tumor lysis syndrome
T_{max}	time to maximum plasma concentration
TSH	thyroid stimulating hormone
ULN	upper limit of normal
Vz/F	oral volume of distribution
WBC	white blood cell (count)
WHO	World Health Organization
WOCBP	women of childbearing potential

Study Synopsis

Protocol Number:	ACE-LY-003
Study Drug:	Acalabrutinib (formerly known as ACP-196)
Protocol Title:	An Open-label, Phase 1b/2 Study of Acalabrutinib Alone or in Combination Therapy in Subjects with B-cell Non-Hodgkin Lymphoma
Phase:	Phase 1b/2
Comparator:	None
Background and Rationale for Study	The majority of indolent lymphomas are mature B-cell lymphomas, including the most common subtype of follicular lymphoma (FL), accounting for approximately 25% of all non-Hodgkin lymphomas (NHLs), followed by marginal zone lymphoma (MZL; approximately 12% of all NHLs). Despite the recent advances in treatments for advanced indolent NHLs, the disease is incurable. Although most patients have had extended survival, a subset of patients have early relapses after therapy or have disease that is refractory to existing therapies. Therefore, safe and effective drug combinations, particularly chemotherapy-free approaches, are being studied in patients with relapsed or refractory (R/R) FL. In contrast to indolent NHLs, a subset of NHLs has an aggressive course. Diffuse large B-cell lymphoma (DLBCL) is the most common form of aggressive NHL in the United States, with an annual incidence that has been rising gradually since the 1990s. A significant proportion of patients with DLBCL are cured with standard chemoimmunotherapy including Rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Nonetheless, for those patients not cured by standard initial therapy, the prognosis remains generally poor, and DLBCL still accounts for the highest number of deaths per year of all the NHL histologies. Acalabrutinib is a potent, highly selective covalent inhibitor of Bruton tyrosine kinase (BTK) in clinical development for B-cell malignancies. Acalabrutinib inhibits B-cell receptor (BCR) signaling by irreversibly inactivating BTK, leading to decreased growth and survival signals in B cells and shows greater kinase selectivity for BTK than ibrutinib in laboratory studies. In laboratory studies, acalabrutinib and its major metabolite, ACP-5862, have limited off-target kinase activity. The lack of activity against other Tec- and Src-family kinases, which are important for the function of T cells, NK cells, and platelets and against epidermal growth factor receptor (EGFR), a kinase important for epithelial cell functions, may contribute to the safety and efficacy profile of acalabrutinib.

	Acalabrutinib has an acceptable safety profile in clinical studies. Acalabrutinib has been administered to subjects with hematologic malignancies, solid tumors, or rheumatoid arthritis, and healthy volunteers or noncancer patients with mild- to moderate-hepatic impairment. Acalabrutinib monotherapy has also demonstrated clinical activity in patients with chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), FL, and DLBCL. For more detailed information on acalabrutinib clinical experience, refer to the Acalabrutinib Investigator Brochure. Rituximab, an anti-cluster of differentiation 20 (CD20) monoclonal antibody, is indicated for treatment of $CD20^+$ NHL as a single agent and in combination with chemotherapy. The combination of rituximab and ibrutinib has been evaluated in a Phase 2 clinical trial in treatment-naive patients with FL. In patients receiving concurrent treatment with ibrutinib and rituximab (n=60), the overall response rate (ORR) was 85%, with complete response (CR) rate of 35%. The 12-month progression-free survival (PFS) was reported as 87%. The drug combination appeared to be well tolerated based on the lack of new safety signals in patients treated with the combination. Moreover, the acceptable safety and efficacy results to date for rituximab and the first-generation BTK inhibitor, ibrutinib, support further evaluation of rituximab with a novel BTK inhibitor such as acalabrutinib. Safety data from Part 1 of the ACE-LY-003 trial are included in the current Acalabrutinib Investigator Brochure. These data show that the combination of acalabrutinib and rituximab is safe and well tolerated in patients with FL. Lenalidomide is an immunomodulatory agent with anti-inflammatory and antiangiogenic properties. In combination with rituximab, lenalidomide has shown promising activity in patients with FL and R/R DLBCL. In an effort to improve clinical benefit, the addition of ibrutinib to the lenalidomide and rituximab regimen has been explored in recent clinical trials. This triplet regimen was evaluated in the frontline treatment of FL, and results showed this triplet regimen was not superior in efficacy than the lenalidomide-rituximab doublet regimen. There are ongoing trials evaluating the triplet combination in R/R DLBCL. These studies support the exploration of acalabrutinib in combination with lenalidomide and rituximab in R/R FL and DLBCL. The purpose Parts 1 and 2 in this study is to evaluate the safety, pharmacokinetics (Part 1), pharmacodynamics, and activity of acalabrutinib alone or in combination with rituximab in subjects with FL or MZL. The purpose of Part 3 of this study is to evaluate the safety, activity, pharmacokinetics, and pharmacodynamics of acalabrutinib in combination with rituximab and lenalidomide in subjects with R/R FL.

Study Design:	This study will be conducted in 3 parts. Note: Text throughout the protocol applies to <u>all parts</u> of the study unless otherwise specified. At the time of Amendment 6, the sponsor made the decision to close Part 4 of the study (R/R DLBCL: Acalabrutinib + rituximab and lenalidomide). **Part 1** This part of the study is a Phase 1b, multicenter, open-label, randomized, parallel group study to be conducted at approximately 11 centers. Two cohorts will be enrolled in parallel: The Relapsed/Refractory Cohort will include approximately 24 subjects with R/R FL, and the Treatment-Naive Cohort will include 12 subjects who have not previously been treated for FL. Note: At the time of Amendment 4, enrollment in Part 1 has been completed. **<u>Relapsed/Refractory Cohort</u>** <u>Arm 1</u>: Acalabrutinib 100 mg by mouth (PO) twice daily (BID) administered approximately 12 hours apart (BID dosing=200 mg total daily dose) for 28 days <u>Arm 2</u>: Acalabrutinib 100 mg PO BID administered approximately 12 hours apart (BID dosing=200 mg total daily dose) for 28 days, plus rituximab 375 mg/m^2 intravenous (IV) on Days 1, 8, 15, and 22 of Cycle 1 and Day 1 of Cycles 2 through 6 **<u>Treatment-Naive Cohort</u>**: A total of 12 subjects will receive the combination of acalabrutinib and rituximab: acalabrutinib 100 mg PO BID administered approximately 12 hours apart (BID dosing=200 mg total daily dose) for 28 days, plus rituximab 375 mg/m^2 IV on Days 1, 8, 15, and 22 of Cycle 1 and Day 1 of Cycles 2 through 6. Pharmacokinetic (PK)/pharmacodynamic (PD) testing will be performed in Cycle 1 and Cycle 2. Tumor assessments will be performed at 8- to 24-week intervals during the trial. Refer to protocol for a comprehensive list of study assessments and their timing. **Part 2** This part of the study is a Phase 2, multicenter, open-label, study to be conducted at approximately 38 centers. Up to 40 subjects with R/R MZL will be enrolled. Each cycle is 28 days. At the time of Amendment 6, the decision was made to close Cohort 2. <u>Cohort 1</u>: Acalabrutinib 100 mg PO BID administered approximately 12 hours apart (BID dosing=200 mg total daily dose) for 28 days <u>Cohort 2</u>: Acalabrutinib 100 mg PO BID administered approximately 12 hours apart (BID dosing=200 mg total daily dose) for 28 days, plus rituximab

	375 mg/m^2 IV on Days 1, 8, 15, and 22 of Cycle 1 and Day 1 of Cycles 2 through 6 See protocol for the Part 2 study schema. Samples for PD and molecular profiling will be collected according to sampling times in the Schedule of Assessments (see protocol). Tumor assessments will be performed at 12- week intervals in the first year and every 24 weeks thereafter during the study. Refer to protocol for a comprehensive list of study assessments and their timing. **Part 3** This is a dose-finding, Phase 1b, multicenter, open-label study to be conducted at approximately 38 centers. Approximately 26 to 32 subjects with R/R FL will be enrolled and treated with acalabrutinib, rituximab, and lenalidomide (each cycle is 28 days). Once a safe and tolerable dose of lenalidomide has been established, 14 subjects (as part of the 26 to 32 subjects total) will be treated on the 3 drugs at that dose of lenalidomide. • Acalabrutinib 100 mg PO BID administered approximately 12 hours apart (BID dosing=200 mg total daily dose), until disease progression or an unacceptable toxicity occurs. • Rituximab 375 mg/m^2 IV administered on Days 1, 8, 15, and 22 of Cycle 1, and Day 1 of every cycle starting at Cycle 2 through Cycle 6, followed by 10 additional doses of maintenance rituximab every other cycle beginning with Cycle 8 for subjects who have not progressed. • Lenalidomide will start at 15 mg PO once a day (QD) for the first 6 subjects in Cycle 1. Doses up to 20 mg PO QD will be explored. Lenalidomide will be administered on Days 1 through 21 of a 28-day cycle. Acalabrutinib has been used in combination with rituximab at the doses mentioned above and this combination has an acceptable safety profile (current version of Acalabrutinib Investigator Brochure). There will be an inter-subject dose escalation or de-escalation during the dose-limiting toxicity (DLT) review period to find the appropriate dose of lenalidomide that can be used in combination with acalabrutinib and rituximab. DLT review and enrollment are presented in a schematic in the protocol for Part 3 and will be conducted as follows (DLT criteria are defined in the protocol): Six subjects are planned to be enrolled initially and treated with acalabrutinib, rituximab, and lenalidomide (15 mg PO QD) in Cycle 1. At the end of the cycle, subjects will be evaluated for DLTs on a rolling basis.

	• If there are ≥2 subjects with DLTs on 15 mg of lenalidomide QD, the dose of lenalidomide will be reduced to 10 mg QD, and 6 more subjects are planned to be enrolled at this reduced dose of lenalidomide.
	  ○ If there are ≥2 subjects with DLTs at the end of Cycle 1 on 10 mg lenalidomide QD, enrollment will close.
	  ○ If there are <2 of 6 subjects with DLTs, then approximately 14 additional subjects will be enrolled and treated with lenalidomide 10 mg QD for Cycles 1 through 12.
	• If there are <2 of 6 subjects with DLTs on 15 mg QD, 6 additional subjects are planned to be enrolled to receive an increased dose of lenalidomide at 20 mg QD.
	  ○ If there are ≥2 subjects with DLTs, the dose of lenalidomide will be reduced back to 15 mg QD. Approximately 14 more subjects will be added to complete enrollment at the 15-mg QD dose.
	  ○ If there are <2 of 6 subjects with DLTs, 20 mg of lenalidomide will be the dose used for Cycles 2 through 12. Approximately 14 more subjects will be added to complete enrollment.
	
	Note: Subjects will be evaluated for DLTs at the end of the first cycle, on a rolling basis, when they complete a cycle of treatment.
	
	Refer to protocol for a comprehensive list of study assessments and their timing.
	
	Part 4
	
	At the time of Amendment 6, the sponsor made the decision to close Part 4 cohort to enrollment. Therefore, Part 4 has been removed.
	
	All Parts
	Twenty-eight days of study drug administration is 1 cycle. Treatment with acalabrutinib may be continued until confirmed disease progression or an unacceptable drug-related toxicity occurs.
	
	Dose modification provisions are provided in the protocol. Note: Temporary withholding of acalabrutinib for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. All subjects who discontinue study drug will have a safety follow-up visit 30 (+7) days after the last dose of study drug until the final data cut-off regardless of whether the subject receives a new anticancer therapy or demonstrates disease progression within this timeframe.
	
	All subjects will have hematology, serum chemistry, hepatitis serology, and urinalysis safety panels performed at screening. For Part 1 and Part 2, once dosing commences (Day 1), all subjects will be evaluated for safety, including hematology and serum chemistry, once weekly for the first

	4 weeks, every 2 weeks in Cycle 2, monthly through Cycle 13, and then every 3 months thereafter. For Part 3, once dosing commences (Day 1), all subjects will be evaluated for safety, including hematology and serum chemistry, once weekly for the first 4 weeks, every 2 weeks in Cycle 2, and monthly through Cycle 13, and for Part 3, every 8 weeks starting Cycle 14 up to cycle 28 (rituximab infusion ends at Cycle 26) and every 3 months thereafter. **Part 3** Pregnancy testing will be performed at baseline, weekly for the first month, and then monthly for all females of childbearing potential receiving lenalidomide until 4 weeks after the last dose of lenalidomide. In addition, women of childbearing potential must use highly effective methods of contraception or abstain from sex during lenalidomide treatment and for 4 weeks after completion of lenalidomide treatment. All subjects (males and females) receiving lenalidomide must be enrolled in the Revlimid® Risk Evaluation and Mitigation Strategy (REMS™) program.
Study Objectives:	**Part 1** **Primary Objective:** • To characterize the safety profile of acalabrutinib alone or in combination with rituximab in subjects with R/R FL **Secondary Objectives:** • To characterize the safety profile of acalabrutinib in combination with rituximab in subjects with previously untreated FL • To characterize the PK profile of acalabrutinib alone or in combination with rituximab • To evaluate the PD effects of acalabrutinib alone or in combination with rituximab • To evaluate the activity of acalabrutinib alone or in combination with rituximab as measured by ORR, duration of response (DOR), time-to-next treatment, and PFS **Part 2** Please note that enrollment for Part 2, Cohort 2 (R/R MZL: Acalabrutinib + Rituximab) of the ACE-LY-003 study is closed. **Primary Objective** • To characterize the activity of acalabrutinib alone or in combination with rituximab in subjects with R/R MZL, as measured by ORR **Secondary Objectives:** • To characterize the safety of acalabrutinib alone or in

	combination with rituximab in subjects with R/R MZL • To evaluate the activity of acalabrutinib alone or in combination with rituximab in subjects with R/R MZL, as measured by DOR, PFS, and overall survival (OS) **Exploratory Objectives:** • [redacted] **Part 3** **Primary Objective** • To characterize the safety of acalabrutinib in combination with rituximab and lenalidomide in subjects with R/R FL **Secondary Objectives:** • To characterize the activity of acalabrutinib in combination with rituximab and lenalidomide in subjects with R/R FL as measured by ORR, DOR, PFS, and OS **Exploratory Objectives:** • [redacted]
Efficacy Parameters:	**Part 1** • ORR • DOR • PFS • Time-to-next treatment **Part 2 and Part 3** • OR

	• DOR • PFS • OS
Safety Parameters:	The safety of acalabrutinib alone or in combination with rituximab or rituximab and lenalidomide will be characterized by the type, frequency, severity, timing of onset, duration, and relationship to study drug of any adverse events (AEs); serious adverse events (SAEs); or AEs leading to study treatment delay, dose modification, or discontinuation.
Definition of Dose-Limiting Toxicity (Part 3)	A DLT will be defined as the occurrence of any of the following study drug-related AEs during the DLT review period. (Note: AEs clearly related to disease progression or the subject's medical history and associated comorbidities considered by the investigator to be unrelated to study drugs, will not be considered DLTs. Infusion reactions clearly associated with rituximab infusion will not be considered DLTs): 1. Non-hematologic DLTs include a) Grades 3 or 4 nausea, vomiting, or diarrhea lasting >7 days despite optimal antiemetic or antidiarrheal management or any Grade 3 or Grade 4 toxicity b) Any grade Stevens-Johnson syndrome or toxic epidermal necrolysis c) Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 × upper limit of normal (ULN) concurrently with total bilirubin >2 × ULN d) Clinical tumor lysis syndrome (TLS) not resolving to baseline after a 2-week treatment delay • Exceptions are deep vein thrombosis (DVT), correctable electrolyte abnormalities, or Grade 3 or Grade 4 laboratory abnormalities lasting ≤7 days; Grades 3 or 4 fatigue, anorexia, non-neutropenic fever, Grade 3 rash resolving to Grade 2 within 10 days (allowed therapy with steroids). 2. Hematologic DLTs a) Grade 3 or Grade 4 neutropenia with fever ≥38.5°C or infection, or Grade 4 neutropenia lasting >7 days despite adequate granulocyte-colony stimulating factor (G-CSF) use. b) Grade 3 or Grade 4 thrombocytopenia with hemorrhage. If thrombocytopenia improves to Grade ≤2 or to ≥80% of the baseline value within 28 days, without a platelet transfusion, this will not be considered a DLT. c) Any Grade 4 hematologic toxicity unrelated to the underlying disease 3. Any study drug-related Grade 5 AE

	Any study drug-related toxicity leading to an individual drug dose delay of >21 consecutive days for acalabrutinib or >14 consecutive days for lenalidomide will be considered as a DLT. Subjects should receive at least one dose of rituximab in Cycle 1 to be evaluable for DLT.
Pharmacokinetic Parameters:	**Part 1** The plasma pharmacokinetics of acalabrutinib in subjects receiving acalabrutinib alone or in combination with rituximab will be characterized using noncompartmental analysis. The following PK parameters will be calculated, whenever possible, from plasma concentrations of acalabrutinib: • AUC_{0-t}: Area under the plasma concentration-time curve calculated using linear trapezoidal summation from time 0 to time t, where t is the time of the last measurable concentration (C_t). • AUC_{0-12}: Area under the plasma concentration-time curve from 0 to 12 hours, calculated using linear trapezoidal summation. • $AUC_{0-\infty}$: Area under the plasma concentration-time curve from 0 to infinity, calculated using the formula: $AUC_{0-\infty}=AUC_{0-t} + C_t / \lambda_z$, where λ_z is the apparent terminal elimination rate constant. • $AUC_{0-24calc}$: Area under the plasma concentration-time curve from 0 to 24 hours, calculated by doubling the value for AUC_{0-12}. • C_{max}: Maximum observed plasma concentration • T_{max}: Time of the maximum plasma concentration (obtained without interpolation) • $t_{½}$: Terminal elimination half-life (whenever possible) • λ_z: Terminal elimination rate constant (whenever possible) • CL/F: Oral clearance • Vz/F: Oral volume of distribution The PK parameters will be tabulated and summarized using descriptive statistics. **Part 2** No PK analysis will be performed in Part 2 **Part 3** Plasma concentrations of acalabrutinib and ACP-5862 will be tabulated for each subject by arm, visit, and timepoint. Summary statistics (mean, median, standard deviation,

	percentage coefficient of variation) and plots will be presented, as appropriate. Additional analyses, including population PK analysis, may be conducted as appropriate.
Pharmacodynamic Parameters and Molecular Profiling:	**Part 1** Standard PK parameters for acalabrutinib in plasma will be evaluated in this study. A full description of the PK parameters is provided in the protocol. The occupancy of BTK by acalabrutinib will be measured in peripheral blood mononuclear cells (PBMCs) and bone marrow, when available, with the aid of an acalabrutinib analogue probe. **Part 2** No PK analysis will be performed in Part 2. The occupancy of BTK by acalabrutinib will be measured in PBMCs and bone marrow, when available, with the aid of an acalabrutinib analogue probe. The effect of acalabrutinib on biologic markers of BTK function will also be evaluated. Molecular profiling of tumor, blood, and bone marrow, when available (including but not limited to BTK mutation), will be performed. **Part 3** Sparse acalabrutinib PK samples will be collected and analyzed to investigate the relationship between acalabrutinib and its active metabolite (ACP-5862) concentration and response. The occupancy of BTK by acalabrutinib will be measured in PBMCs and bone marrow, when available, with the aid of an acalabrutinib analogue probe. [redacted]
Sample Size:	**Part 1** A total of 24 subjects (12 each arm) in the Relapsed/Refractory Cohort will be equally randomized into 1 of 2 treatment arms (monotherapy and combination therapy). Twelve subjects will be enrolled to the Treatment-Naive Cohort receiving the combination therapy. **Part 2** Part 2 will enroll up to 40 subjects in Cohort 1. **Part 3** A total of approximately 26 to 32 subjects are to be enrolled in Part 3.
Inclusion Criteria:	Eligible subjects will be considered for inclusion in this study if they meet **all** of the following criteria. **Part 1** 1. Men and women ≥18 years of age.

	2. Relapsed/Refractory Cohort: A confirmed diagnosis of FL Grade 1, 2, or 3a that has relapsed after, or been refractory to ≥1 prior therapy for FL and which requires treatment per National Cancer Institute or International Working Group guidelines. Documented failure to achieve at least partial remission (PR) with, or documented disease progression after, the most recent treatment regimen. Treatment-Naive Cohort: A confirmed diagnosis of FL Grade 1, 2, or 3a that requires treatment per National Cancer Institute or International Working Group guidelines in subjects who have not previously received systemic anticancer therapy for FL. 3. Presence of radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (defined as the presence of ≥1 lesion that measures ≥2.0 cm in the longest dimension and ≥1.0 cm in the longest perpendicular dimension as assessed by computed tomography [CT] scan). 4. Eastern Cooperative Oncology Group (ECOG) performance status of ≤2. 5. Agreement to use highly effective methods of contraception during the study and for 2 days after the last dose of acalabrutinib or 12 months after the last dose of rituximab, whichever is longer, if sexually active and able to bear or beget children. Highly effective forms of contraception are defined in the protocol. 6. Men must agree to refrain from sperm donation during the study and for 3 months after the last dose of rituximab. 7. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules or tablets without difficulty. 8. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local patient privacy regulations). **Part 2** 1. Men and women ≥18 years of age. 2. Histologically confirmed MZL including splenic, nodal, and extranodal sub-types a. Subjects with splenic MZL must have an additional measurable lesion, nodal or extranodal, as described in inclusion criterion #4; b. Subjects with gastric mucosa-associated lymphoid tissue (MALT) lymphoma must be Helicobacter pylori-negative (including subjects after successful elimination of H. pylori) or refractory to H. pylori eradication therapy by a minimum time of 12 months

	by a pathology confirmation or by a ^{13}C urea test (proton-pump inhibitors and H2 blockers should be discontinued or withheld for at least 14 days and 7 days, respectively, and antibiotics for treating H. pylori, such as those with anti-helicobacter action and bismuth preparations, should be withdrawn at least 30 days before H. pylori testing). 3. Previous therapy: a. Cohort 1: Previously received 1 or more lines of systemic therapy including at least 1 CD20-directed regimen (either as monotherapy or as chemoimmunotherapy for MZL) with documented failure to achieve at least PR, or documented disease progression after the most recent treatment regimen. b. Cohort 2: Previously received 1 or more lines of therapy including at least 1 prior systemic therapy for MZL **or** radiation therapy with documented failure to achieve at least PR, or documented disease progression after the most recent treatment regimen. 4. Presence of radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (defined as the presence of ≥1 lesion that measures ≥2.0 cm in the longest dimension and ≥1.0 cm in the longest perpendicular dimension as assessed by CT scan). Lesions in anatomical locations, such as extremities or soft tissue lesions, that are not well visualized by CT may be measured by magnetic resonance imaging (MRI) instead; subjects with spleen- only disease are considered as not having measurable disease. 5. ECOG performance status of ≤2. 6. Women must agree to use highly effective methods of contraception during the study and for 2 days after the last dose of acalabrutinib or 12 months after the last dose of rituximab, whichever is longer, if sexually active and able to bear or beget children. Highly effective methods of contraception are defined in the protocol. 7. Men must agree to refrain from sperm donation during the study and for 3 months after the last dose of rituximab. 8. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules or tablets without difficulty. 9. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national patient privacy regulations). **Part 3** 1. Men and women ≥18 years of age

	2. For subjects with FL: Pathologically confirmed diagnosis of FL Grade 1, 2, or 3a that has relapsed after, or been refractory to ≥1 prior therapy for FL and which requires treatment per National Cancer Institute or European Society for Medical Oncology (ESMO) clinical practice guidelines. 3. This criterion was removed under Amendment 6. 4. Subjects must have previously received at least 1 frontline standard chemoimmunotherapy regimen. 5. Subjects with suspected residual disease after the treatment regimen directly preceding study enrollment must have biopsy-demonstrated residual FL. 6. Documented R/R disease, defined as either: 1) recurrence of disease after a CR or PR, or 2) stable disease or progressive disease at completion of the treatment regimen preceding entry to the study (residual disease). 7. Presence of radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (defined as the presence of ≥1 lesion that measures ≥2.0 cm in the longest dimension and ≥1.0 cm in the longest perpendicular dimension as assessed by CT scan). 8. ECOG performance status of ≤2. 9. Females of reproductive potential must a. have 2 negative pregnancy tests prior to initiating treatment with lenalidomide. The first should be within 10 to 14 days and the second test within 24 hours prior to first dose of lenalidomide. b. commit to abstain continuously from heterosexual sex or use highly effective methods of contraception. Contraception must be used beginning 4 weeks prior to initiating treatment with lenalidomide, during therapy with any study drug, and during dose interruptions for lenalidomide. Contraception must be used for 2 days after the last dose of acalabrutinib,12 months after the last dose of rituximab, or 4 weeks after the last dose of lenalidomide, whichever is later 10. Men must agree to use a synthetic or latex condom during any sexual contact with female of reproductive potential including with pregnant partners while taking lenalidomide and for up to 4 weeks after last dose of lenalidomide, even if they have undergone a successful vasectomy. Men must agree to refrain from sperm donation during the study and for 3 months after the last dose of rituximab or 4 weeks after the last dose of lenalidomide, whichever is later. 11. Subjects must not donate blood during treatment with lenalidomide and for 4 weeks after discontinuation of lenalidomide. 12. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules or tablets without difficulty.

	13. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national patient privacy regulations).
Exclusion Criteria:	Subjects will be ineligible for this study if they meet **any** of the following criteria. **Part 1** 1. Prior malignancy (other than indolent B-cell NHL), except for adequately treated basal cell or squamous cell skin cancer, in situ cancer, or other cancer from which the subject has been disease free for ≥2 years. 2. Known CNS lymphoma or leptomeningeal disease. 3. A life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of acalabrutinib, or put the study outcomes at undue risk. 4. Known history of a bleeding diathesis (e.g., hemophilia, von Willebrand disease). 5. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or corrected QT interval (QTc) >480 msec. 6. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, gastric bypass, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction. 7. Any immunotherapy within 4 weeks of first dose of study drug. 8. Relapsed/Refractory Cohort: The time from the last dose of the most recent chemotherapy or experimental therapy to the first dose of study drug is <5 times the half-life of the previously administered agent(s). 9. Prior exposure to a BCR inhibitor (e.g., BTK, phosphonositide-3 kinase [PI3K], or spleen tyrosine kinase [SYK] inhibitors) or BCL-2 inhibitor (e.g., venetoclax). 10. Known history of anaphylaxis or hypersensitivity to rituximab (Rituxan/MabThera) or any of its components. 11. Ongoing immunosuppressive therapy, including systemic or enteric corticosteroids for treatment of FL or other conditions. Note: Subjects may use topical or inhaled corticosteroids or low-dose steroids (≤20 mg of prednisone or equivalent) as therapy for comorbid conditions. During study participation, subjects may also receive systemic or enteric corticosteroids

	as needed for treatment-emergent comorbid conditions. 12. Grade ≥2 toxicity (other than alopecia) continuing from prior anticancer therapy including radiation. 13. Known history of HIV or active infection with hepatitis C virus (HCV) or any uncontrolled active systemic infection. 14. Known hepatitis B infection or positive for hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (anti-HBc). Since intravenous immunoglobulins (IVIG) may cause false positive hepatitis serology, subjects who are receiving prophylactic IVIG and have positive HBsAg or anti-HBc must have negative hepatitis B DNA to be eligible. 15. Major surgery within 4 weeks before first dose of acalabrutinib. 16. Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenia purpura. 17. History of stroke or intracranial hemorrhage within 6 months before the first dose of acalabrutinib. 18. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonist (e.g., phenprocoumon) within 7 days of first dose of study drug. 19. Requires treatment with proton-pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). Note: this criterion no longer applies to patients who have switched from acalabrutinib capsules to tablets. 20. Received a live virus vaccination within 28 days of first dose of study drug. 21. ANC $<0.75 \times 10^9$/L or platelet count $<50 \times 10^9$/L. For subjects with documented disease involvement in the bone marrow, ANC $<0.50 \times 10^9$/L or platelet count $<30 \times 10^9$/L. 22. Creatinine >2.5 × institutional ULN; total bilirubin >2.5 × ULN; and AST or ALT >3.0 × ULN. 23. Breastfeeding or pregnant. 24. Concurrent participation in another therapeutic clinical trial. 25. Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before screening. **Part 2** 1. Prior malignancy (other than indolent B-cell NHL), except for adequately treated basal cell or squamous cell skin cancer, in situ cancer, or other cancer from which the subject has been disease free for ≥2 years. 2. Known medically apparent CNS lymphoma or

	leptomeningeal disease. 3. Known evidence of transformation to another aggressive lymphoma. 4. A life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of acalabrutinib, or put the study outcomes at undue risk. 5. Known history of a bleeding diathesis (e.g., hemophilia, von Willebrand disease). 6. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or QTc using Fridericia formula (QTcF) >480 msec. 7. Malabsorption syndrome, disease significantly affecting gastrointestinal function (excluding gastric MALT), or resection of the stomach or small bowel, gastric bypass, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction. 8. This criterion was removed under Amendment 5. 9. This criterion was removed under Amendment 5. 10. Prior exposure to a BCR inhibitor (e.g., BTK or SYK inhibitors). 11. For Cohort 2, evidence of CD20− MZL and/or known history of anaphylaxis or hypersensitivity to rituximab (Rituxan/MabThera) or any of its components. 12. Ongoing immunosuppressive therapy, including systemic or enteric corticosteroids for treatment or other conditions within 1 week before the first dose of study drug. Note: Subjects may use topical or inhaled corticosteroids or low-dose steroids (≤20 mg of prednisone or equivalent for up to 2 weeks) as therapy for comorbid conditions. However, subjects requiring systemic steroids at daily doses >20 mg prednisone equivalent of systemic exposure are not allowed. 13. Grade ≥2 toxicity (other than alopecia or laboratory value requirements mentioned in Part 2) continuing from prior anticancer therapy including radiation. 14. Uncontrolled active systemic fungal, bacterial, viral, or other infection (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment), or intravenous anti-infective treatment within 2 weeks before first dose of study drug. 15. Known history of infection with HIV. 16. Serologic status reflecting active hepatitis B or C infection.

	• Subjects who are anti-HBc positive and who are surface antigen negative will need to have a negative hepatitis B virus (HBV) DNA polymerase chain reaction (PCR) result before enrollment. Subjects who are HBsAg positive or hepatitis B PCR positive will be excluded. • Subjects who are anti-HCV positive will need to have a negative PCR result before enrollment. Subjects who are hepatitis C PCR positive will be excluded. 17. History of allogeneic stem cell (or organ) transplantation. 18. This criterion was removed under Amendment 5. 19. Major surgery within 4 weeks before first dose of acalabrutinib. 20. Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenia purpura. 21. History of stroke or intracranial hemorrhage within 6 months before the first dose of acalabrutinib. 22. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonist (e.g., phenprocoumon) within 7 days of first dose of study drug. 23. Requires treatment with proton-pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). Note: this criterion no longer applies to patients who have switched from acalabrutinib capsules to tablets. 24. Received a live virus vaccination within 28 days of first dose of study drug. 25. ANC $<1.0 \times 10^9$/L or platelet count $<100 \times 10^9$/L. For subjects with documented disease involvement in the bone marrow, ANC $<0.50 \times 10^9$/L or platelet count $<30 \times 10^9$/L. 26. Creatinine >1.5 × institutional ULN; total bilirubin >1.5 × ULN; and AST or ALT >2.5 × ULN. 27. Breastfeeding or pregnant. 28. Concurrent participation in another therapeutic clinical trial. 29. In the absence of gastric MALT (subject to inclusion criterion 2b) presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before screening or diagnosed >3 months before screening and without confirmed resolution by endoscopy. 30. Received any chemotherapy, external beam radiation therapy, anticancer antibodies, or investigational drug within 30 days before first dose of study drug. 31. History of or ongoing progressive multifocal leukoencephalopathy (PML).

	Part 3 1. Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cancer, or other cancer from which the subject has been disease free for ≥2 years. 2. Subjects for whom the goal of therapy is tumor debulking before stem cell transplant. 3. Known history or presence of CNS lymphoma or leptomeningeal disease. 4. Transformed DLBCL or DLBCL with coexistent histologies (e.g., FL or mucosa-associated lymphoid tissue and primary mediastinal large B-cell lymphoma (PMBCL). 5. A life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of acalabrutinib, or put the study outcomes at undue risk. 6. Known history of a bleeding diathesis (e.g., hemophilia, von Willebrand disease). 7. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or QTcF >480 msec. Exception: Subjects with controlled, asymptomatic atrial fibrillation during screening are allowed to be enrolled on study. 8. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, gastric bypass, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction. 9. Received any chemotherapy, external beam radiation therapy, anticancer antibodies, or investigational drug within 30 days before first dose of study drug. 10. Prior exposure to a BCR inhibitor (e.g., BTK or SYK inhibitors), lenalidomide, or CAR-T cell therapy. 11. Known history of anaphylaxis or hypersensitivity to rituximab (Rituxan/MabThera) or any of its components. 12. Subjects with a prior history of Grade 4 rash associated with thalidomide treatment. 13. Ongoing immunosuppressive therapy, including systemic (e.g., IV or oral) corticosteroids within 2 weeks before the first dose of study drug. Note: Subjects may use topical or inhaled corticosteroids or low-dose steroids (≤20 mg prednisone equivalent/day for ≤2 weeks) as a therapy for comorbid

	conditions. During study participation, subjects may also receive systemic (e.g., IV or oral) corticosteroids as needed for treatment-emergent comorbid conditions. 14. Grade ≥2 toxicity (other than alopecia or laboratory value requirements mentioned in Part 3 exclusion criteria) continuing from prior anticancer therapy including radiation. 15. Uncontrolled active systemic fungal, bacterial, viral, or other infection (defined as exhibiting ongoing signs or symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment), or intravenous anti-infective treatment within 2 weeks before first dose of study drug. 16. Known history of infection with HIV. 17. Serologic status reflecting active hepatitis B or C infection. a. Subjects who are anti-HBc positive and who are surface antigen negative will need to have a negative PCR result before enrollment. Subjects who are HBsAg positive or hepatitis B PCR positive will be excluded. b. Subjects who are HCV antibody (anti-HCV) positive will need to have a negative PCR result before enrollment. Subjects who are HCV PCR positive will be excluded. 18. History of allogeneic stem cell (or organ) transplantation. 19. Major surgery within 4 weeks before first dose of acalabrutinib. 20. Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenia purpura. 21. History of stroke or intracranial hemorrhage within 6 months before the first dose of acalabrutinib. 22. Requires or has received anticoagulation with warfarin or equivalent vitamin K antagonist (e.g., phenprocoumon) within 7 days of first dose of study drug. 23. Received a live virus vaccination within 28 days of first dose of study drug. 24. ANC <1.0 × 10^9/L or platelet count <75 × 10^9/L. Subjects will only be considered eligible if peripheral blood counts can be maintained independent of growth factors or transfusions during screening. 25. Creatinine clearance of <60 mL/min, calculated using the formula of Cockcroft and Gault [(140-Age) * Mass (kg)/(72 * creatinine mg/dL) * 0.85 if female]. 26. Total bilirubin >1.5 × ULN, or AST or ALT >2.5 × ULN, unless directly attributable to Gilbert's syndrome. 27. Total bilirubin >1.5 × ULN, or AST or ALT >2.5 × ULN,

	unless directly attributable to Gilbert's syndrome. 28. Requires treatment with proton-pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole or pantoprazole). Subject receiving proton-pump inhibitors who switch to H2-receptor antagonists or antacids are eligible for enrollment to this study. Note: this criterion no longer applies to patients who have switched from acalabrutinib capsules to tablets. 29. Breastfeeding or pregnant. 30. Concurrent participation in another therapeutic clinical trial. 31. History of or ongoing PML.
Dosage Form and Strength:	As of Clinical Study Protocol (CSP) Version 8.0, acalabrutinib is supplied in 2 formulations (hard gelatin capsules and orange film coated tablets) for oral administration, prepared using standard pharmaceutical grade excipients. Acalabrutinib capsules and tablets are bioequivalent in relation to dosage strength. Acalabrutinib will be provided in white, high-density polyethylene bottles. Rituximab (Rituxan/MabThera) injection is a commercial product (Genentech, Inc., South San Francisco, CA/Roche, Basal Switzerland). Rituximab is available in 100 mg/10 mL single-use vials and 500 mg/50 mL single-use vials. Lenalidomide (Revlimid) is a commercial product (Celgene, Inc, Summit, NJ). Lenalidomide is available as capsules containing 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg of drug substance. Refer to product information from the manufacturers for details on formulation, packaging, and storage of rituximab and lenalidomide.
Dose Regimen/Route of Administration:	Acalabrutinib is intended to be administered orally with 8 ounces (approximately 240 mL) of water. Acalabrutinib taken with an acidic beverage may impact exposure to acalabrutinib (refer to the current Acalabrutinib Investigator Brochure). Acalabrutinib may be administered without regard to food. The capsules or tablets should be swallowed intact and subjects should not attempt to open capsules or crush tablets, and both formulations should not be dissolved in water. Acalabrutinib should be taken BID, approximately 12 hours apart. Rituximab is to be administered as an IV infusion, not an IV push or bolus. Detailed instructions for the preparation and administration of rituximab are provided in the Rituxan/MabThera package insert and per institutional standards. No dose reductions for rituximab are allowed. On days when both acalabrutinib and rituximab are administered, the rituximab infusion should begin approximately 1 hour after the acalabrutinib dose. **Part 3** Lenalidomide is to be administered orally at approximately the same time each day, either with or without food. The capsules

	should be swallowed whole with water. The capsules should not be opened, broken, or chewed. Lenalidomide is administered for the first 21 days of each 28-day cycle. On days that both acalabrutinib and lenalidomide are administered, lenalidomide should be taken approximately 30 minutes prior to the first daily dose of acalabrutinib. Dose modification provisions are provided in the protocol.
Concomitant Medications:	The concomitant use of strong inhibitors/inducers of CYP3A (see protocol) should be avoided when possible. Acalabrutinib is a substrate of CYP3A4. Drugs inhibiting CYP3A may increase exposure of acalabrutinib. If a subject requires short-term treatment with a strong CYP3A inhibitor (such as anti-infectives for up to 7 days), interrupt acalabrutinib treatment. If a subject requires a moderate CYP3A inhibitor while on study, monitor the subject closely for potential toxicities. Conversely, concomitant administration of a strong inducer of CYP3A has the potential to decrease exposure of acalabrutinib and could reduce efficacy. Avoid coadministration of strong CYP3A inducers. 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. Use of proton-pump inhibitors, H2 receptor antagonists, or antacids while taking acalabrutinib capsules 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 capsules) or antacid (2 hours before or 2 hours after acalabrutinib capsules). Avoid coadministration of proton-pump inhibitors with acalabrutinib capsules. Acalabrutinib maleate tablets can be taken without regards to acid-reducing agents (such as antacids, H2-receptor antagonists, or proton-pump inhibitors). **<u>Lenalidomide</u>** Subjects who are concurrently receiving digoxin should have periodic monitoring of digoxin plasma levels is due to increased C_{max} and AUC_{inf} of digoxin with concomitant lenalidomide therapy. Moreover, subjects taking concomitant therapies such as erythropoietin-stimulating agents or estrogen-containing therapies, along with lenalidomide, may have an increased risk of venous thromboembolic events per package insert. **<u>Rituximab</u>** The only drug-drug interaction with rituximab listed in the Rituxan/MabThera package insert is renal toxicity when used in combination with cisplatin.
Statistics:	Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions for discrete variables) will be used to summarize data as appropriate. All analyses will be done by indication, treatment, and overall.

	Part 1 This study will assess acalabrutinib safety, PK, PD, and antitumor activity when administered alone or in combination with rituximab. The primary objective of this study is to determine the safety as such: • With a total sample size of 36, the probability of observing one or more instances of an AE with a background rate of 5% and 10% is 84% and 98%, respectively. • For each treatment arm (n=12 each), the probability of observing one or more instances of an AE with a background rate of 5% and 10% is 46% and 72%, respectively. **Part 2** The primary objective is to characterize the activity of acalabrutinib alone in subjects with R/R MZL as measured by the ORR. Up to 40 subjects in treatment Cohort 1 will provide data for an initial assessment of safety and efficacy of acalabrutinib treatment. Sample size is not based on statistical power consideration. **Part 3** This sample size will provide adequate data for an initial assessment of safety and efficacy of acalabrutinib treatment in combination with lenalidomide and rituximab. This sample size is not based on statistical power consideration.

1 BACKGROUND INFORMATION

1.1 ROLE OF BTK IN LYMPHOID CANCERS

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

Non-Hodgkin lymphoma (NHL) is a diverse class of neoplasms that can originate in B cells, T cells, or natural killer (NK) cells. Estimated new cases and deaths from NHL are 72,240 and 20,140, respectively, in the United States in 2017 (National Cancer Institute 2017). NHL can be divided into two prognostic groups: indolent and aggressive lymphomas. Of the NHLs, indolent NHLs account for 40% of all NHL cases (Leukemia and Lymphoma Society 2008). The majority of indolent lymphomas are mature B-cell lymphomas, including the most common subtype of follicular lymphoma (FL), accounting for approximately 25% of all NHLs (Sehn 2016), followed by marginal zone lymphoma (MZL; approximately 12% of all NHLs; California Cancer Care 2017). MZL can be classified into 3 subtypes: 1) splenic MZL, 2) nodal MZL, and 3) extranodal MZL of mucosa-associated lymphoid tissue (MALT) lymphoma, which is further categorized into gastric MALT and nongastric MALT lymphomas (Swerdlow et al. 2016). In most cases the etiology for indolent lymphomas is unknown, however, associations have been made between indolent NHL and certain immune disorders and microbial pathogens, e.g., gastric MALT is strongly associated with H. pylori infection and splenic MZL with hepatitis C infection (Arcaini et al. 2016, Sehn et al. 2016, Thieblemont et al. 2016, Zucca et al. 2016).

Despite the recent advances in treatments for advanced indolent NHLs, the disease is incurable. Although most patients have had extended survival, a subset of patients have early relapses after therapy or have disease that is refractory to existing therapies (Sehn et al. 2016). Therefore, safe and effective drug combinations, particularly chemotherapy-free approaches, are being studied in patients with

relapsed or refractory (R/R) FL (Sehn et al. 2016). Current approaches to patients with R/R FL vary widely (National Comprehensive Cancer Network 2018), although most combinations include an anti-cluster of differentiation (CD) 20 antibody. Commonly used combination regimens include bendamustine with anti-CD20 (rituximab or obinutuzumab), rituximab added to an anthracycline-based combination chemotherapy (e.g., cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP]; National Comprehensive Cancer Network 2018). Single agent PI3-kinase inhibitors such as idelalisib and copanlisib are currently Food and Drug Administration (FDA)-approved for treatment of patients with FL who have failed 2 prior lines of therapy (ZYDELIG® [prescribing information] 2016; Aliqopa package insert 2017).

In contrast to indolent NHLs, a subset of NHLs has an aggressive course. Diffuse large B-cell lymphoma is the most common form of aggressive NHL in the United States, with an annual incidence that has been rising gradually since the 1990s. A significant proportion of patients with diffuse large B-cell lymphoma (DLBCL) are cured with standard chemoimmunotherapy including Rituximab-CHOP (R-CHOP) (Coiffier et al. 2002, Habermann et al. 2006, Pfreundschuh et al. 2006). Nonetheless, for those patients not cured by standard initial therapy, the prognosis remains generally poor, and DLBCL still accounts for the highest number of deaths per year of all the NHL histologies.

For patients with either refractory or recurrent DLBCL following initial therapy, the approach of re-induction chemotherapy, followed by high-dose chemotherapy with autologous stem cell transplantation (HDT/ASCT) for responding patients, remains the current standard of care. Such an approach was demonstrated to result in superior disease-free survival compared with re-induction chemotherapy alone in a randomized Phase 3 trial (Philip et al. 1995). However, the results of a more recently reported Phase 3 trial comparing rituximab, ifosfamide, carboplatin, and etopside (R-ICE) to rituximab, cisplatin, cytarabine, and dexamethasone (R-DHAP) as re-induction therapy suggests that this standard salvage approach may be less efficacious in the era of rituximab-based first-line therapy, as 3-year event-free survival rates were significantly lower for patients who had received rituximab-based first-line therapy (Gisselbrecht et al. 2010). In addition, HDT/ASCT is associated with considerable treatment-related morbidity and occasional treatment-related mortality. Advanced age and suboptimal baseline pulmonary or cardiac function are risks for excessive morbidity during and after HDT/ASCT. Therefore, effective and tolerable

therapies are needed in R/R DLBCL, particularly in the era of rituximab-based initial chemoimmunotherapy.

There are two major subtypes of DLBCL that are named according to their cell of origin and include germinal center B-cell like (GCB) and activated B-cell like (ABC) subtypes (approximately15% of patients are not classifiable into either subtype, based on gene expression profiling; Alizadeh et al. 2000, Rosenwald et al. 2002). These subtypes are postulated to reflect different oncogenic mechanisms and responses to treatment (Sehn et al. 2015). For example, ABC subtype has worse outcomes following R-CHOP (Lenz et al. 2008). Bortezomib, a proteasome inhibitor of the nuclear factor kappa beta (NFkB) pathway, has demonstrated benefit in ABC subtype and agents such as lenalidomide appear to have activity in non-GCB DLBCL (Dunleavy et al. 2009, Witzig et al. 2011).

Clinical studies have shown that targeting the B-cell receptor (BCR) signaling pathway by inhibiting BTK produces significant clinical benefit in patients with NHL. A first-in-human (FIH) study of ibrutinib in FL showed that 6 of 16 subjects (38%) had an objective response (Fowler et al. 2012). In a Phase 2 trial of patients with R/R FL treated with ibrutinib, the overall response rate (ORR) was 37.5%, with a complete remission (CR) rate of 12.5%, and a median progression-free survival (PFS) of 14 months (Bartlett et al. 2014; Bartlett). Interim results from a Phase 2 study of ibrutinib in subjects with R/R GCB and ABC DLBCL reported an ORR of 41% (CR 17%) for subjects with ABC DLBCL versus 5% (no CRs) for subjects with GCB DLBCL (Wilson et al. 2015). Similar results were observed with ONO-4059, a second generation BTK inhibitor in a Phase 1 dose-escalation study in subjects with ABC DLBCL (Dyer et al. 2014). In both studies, the BTK inhibitors were well tolerated. In recent years, ibrutinib has been approved for the treatment of MZL and Phase 3 studies for ibrutinib are currently ongoing in FL and DLBCL (NCT02947347, NCT01974440, NCT01855750). Moreover, in our experience, acalabrutinib monotherapy showed an ORR of 33% in R/R FL and an ORR of 24% in DLBCL (Dyer et al. 2018, Fowler et al. 2018). The activity of BTK inhibitors in NHL supports the study of acalabrutinib in these NHL histologies.

In a Phase 2, open-label study of ibrutinib, 63 subjects with R/R MZL received ibrutinib at 560 mg orally once daily, including subjects with MZL of MALT lymphoma (n=32), nodal MZL (n=17), and splenic MZL (n=14) (Inman et al. 2017). All subjects had received one or more prior therapies, including an anti-CD20 antibody. All

subjects had an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2 and 33% had bone marrow involvement. Of the 63 patients that were analyzed for efficacy, the ORR was 46%, including a CR in 2 subjects (3.2%). The ORR for the MZL subtypes were as follows: 46.9% (MALT), 41.2% (nodal), and 50% (splenic).

The median time to response was 4.5 months (range 2.3 to 16.4 months). The median PFS was 14.2 months with ibrutinib (95% CI, 8.3-not reported) and the median overall survival (OS) was not yet reached at a median follow-up of 19.4 months. Based on this study, ibrutinib received an accelerated approval for treatment of MZL in patients who have received at least 1 prior anti-CD20 therapy (IMBRUVICA® package insert).

While highly potent in inhibiting BTK, ibrutinib has also shown in vitro activity against other kinases with a cysteine in the same position as Cys481 in BTK to which the drug covalently binds. The inhibition of epidermal growth factor receptor (EGFR) is also observed in cellular assays and may contribute to ibrutinib-related adverse events (AEs) of diarrhea and rash (IMBRUVICA® package insert). In addition, ibrutinib is a substrate for cytochrome P450 (CYP) 3A; inhibition of CYP3A causes a 29-fold increase in maximum observed plasma concentration (C_{max}) and 24-fold increase in area under the curve (AUC) for ibrutinib (IMBRUVICA® package insert). This increases the possibility of drug-drug interactions in combination therapies with drugs currently used in management of subjects with cancer. These limitations support the development of alternative BTK inhibitors for use in the therapy of B-cell malignancies.

Chemical optimization, pharmacologic characterization, and toxicologic evaluation have led to identification of acalabrutinib, an orally administered, new chemical entity that covalently inhibits BTK and shows activity and acceptable safety in nonclinical studies. Acalabrutinib is a potent, highly selective covalent inhibitor of BTK in clinical development for B-cell malignancies. Acalabrutinib inhibits BCR signaling by irreversibly inactivating BTK, leading to decreased growth and survival signals in B-cells and shows greater kinase selectivity for BTK than ibrutinib in laboratory studies. In laboratory studies, acalabrutinib and its major metabolite, ACP-5862, have limited off-target kinase activity (Byrd et al. 2016, 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. Key nonclinical differentiators of acalabrutinib versus ibrutinib are:

- [redacted]
- Acalabrutinib and ibrutinib have been evaluated in NK cell functional assays. While ibrutinib inhibits NK cell functions including antibody-dependent cellular cytotoxicity, lytic granule release, and cytokine production (Kohrt et al. 2014), the in vitro functional activity of acalabrutinib-treated NK cells was preserved.
- Acalabrutinib has been evaluated against ibrutinib in an in vivo thrombus formation model. Platelets from patients with chronic lymphocytic leukemia (CLL) treated with acalabrutinib had similar thrombus formation dynamics as untreated platelets from healthy volunteers, while platelets from ibrutinib-treated patients with CLL had impaired thrombus formation (Byrd et al. 2016).

The nonclinical and toxicology results of acalabrutinib suggest that it may have an improved therapeutic window relative to ibrutinib; it may be more readily combined with other agents for the treatment of cancer.

1.2 NONCLINICAL STUDIES OF ACALABRUTINIB

Summaries of nonclinical studies are provided below. For more detailed information please refer to the Acalabrutinib Investigator Brochure.

1.2.1 Chemistry

Acalabrutinib is an imidazopyrazine analogue with a molecular weight of 465.5 g/mol. The compound has 1 stereogenic center and acalabrutinib is the S-enantiomer.

Acalabrutinib is orally bioavailable in animals and is suitable for formulating in capsules and tablets (as the maleate salt). For clinical testing, acalabrutinib has been manufactured and formulated according to current Good Manufacturing Practices (cGMP).

New Formulation: Acalabrutinib Maleate Tablet

A new film-coated tablet formulation for oral administration, containing acalabrutinib maleate equivalent to 100 mg of acalabrutinib, has been developed and was first approved by the FDA.

Acalabrutinib maleate tablets were shown to be bioequivalent to acalabrutinib capsules in the fasted state in healthy volunteers (Study D8223C00013). Geometric mean PK exposures (C_{max} and AUC_{last} or AUC_{inf}) of acalabrutinib and its metabolite (ACP-5862) were similar (<4% difference) following administration of acalabrutinib maleate tablets and acalabrutinib capsules. In addition, the 90% confidence intervals for geometric mean ratios (C_{max} and AUC_{last} or AUC_{inf}) for acalabrutinib and ACP-5862 were well contained within the range of 80.00% and 125.00%, thus meeting the pre-defined criteria for the conclusion of bioequivalence.

For acalabrutinib maleate tablets, food reduced acalabrutinib C_{max} by approximately 54%, with no effect on AUC (Study D8220C00018). Similar results were observed for ACP-5862. There were no differences in BTK Target Occupancy (BTK-TO) across treatments. The decrease in the rate of exposure, without a change in the extent of exposure or BTK TO, is not considered clinically significant. Overall, these results are consistent with those observed following administration of 100 mg acalabrutinib capsule with food (refer to the CALQUENCE label). Thus, acalabrutinib maleate tablets can be taken with or without food.

1.2.2 Efficacy Pharmacology

Spontaneous canine B-cell lymphoma shares many characteristics with human NHL, including diagnostic classifications and response to BTK inhibition (Honigberg et al. 2010). The life expectancy in untreated animals with aggressive disease is ~6 weeks, thus enabling rapid assessment of drug efficacy (Vail et al. 2004). Acalabrutinib was evaluated in a dose-escalation study in canine spontaneous B-cell lymphoma (Harrington et al. 2016). Twenty dogs were enrolled in the clinical trial and treated with acalabrutinib dosages of 2.5 to 20 mg/kg every 12 or 24 hours. Acalabrutinib was generally well tolerated, with AEs consisting primarily of Grade 1 or Grade 2 anorexia, weight loss, vomiting, diarrhea, and lethargy. Per Veterinary Cooperative Oncology Group criteria for assessment of response in peripheral nodal lymphoma (Vail et al. 2010), the ORR was 25% (5/20 dogs) with a median PFS of 22.5 days.
Clinical benefit was observed in 30% (6/20) of dogs. These findings suggest that acalabrutinib is safe and exhibits activity in canine B-cell lymphoma patients and support the use of canine lymphoma as a relevant model for human NHL. These

findings are similar to the clinical responses (i.e., 1 dog with partial remission [PR] out of 5 dogs treated with suspected or confirmed DLBCL observed with ibrutinib in dogs with spontaneous B-cell lymphoma; Honigberg et al. 2010).

1.2.3 Safety Pharmacology

In vitro and in vivo safety pharmacology studies with acalabrutinib have demonstrated a favorable nonclinical safety profile. Please refer to the Acalabrutinib Investigator Brochure for a detailed review of the nonclinical toxicology program.

1.2.4 Drug-Drug Interaction Potential

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

Please refer to Section 3.7.5 for guidance on drugs that may cause drug-drug interactions.

1.2.5 In Vivo General Toxicology

The systemic toxicity of acalabrutinib has been fully evaluated in repeat-dose studies in mice, rats, and dogs; reproductive toxicity studies in rats and rabbits; and ongoing chronic studies in rats and dogs with durations of up to 28 days, 6 months, and 9 months, respectively; and in reproductive toxicity studies in rats and rabbits. The pivotal Good Laboratory Practice (GLP) studies were chronic studies in rats and dogs, each with recovery periods to assess the reversibility of observed changes. Please refer to the Acalabrutinib Investigator Brochure for a detailed review of the nonclinical toxicology program.

In rats, 100 mg/kg/day was selected initially to represent the highest non-severely toxic dose; however, 100 mg/kg/day was subsequently determined to be a no observed adverse effect level (NOAEL) for male rats, and 30 mg/kg/day was the NOAEL for female rats treated chronically (6-month study). In rats, the target organs of toxicity were kidney, liver, and heart.

The NOAEL in dogs was 30 mg/kg/day; dose levels higher than 30 mg/kg/day were not tolerated. In dogs, the target organs of toxicity, observed only at doses exceeding the maximum tolerated dose, were the kidney and liver. Heart findings were also observed in 2 dogs with a kidney toxicity, which were interpreted as possibly secondary to uremia, as has been reported for this species.

In rats and dogs, no adverse ECG or histopathologic cardiovascular effects were

noted at the planned conclusion of the subchronic general toxicity studies or in the rat chronic toxicity study. However, in rats that have died prematurely at doses of 200 or 300 mg/kg/day, slight to moderate necrosis of the myocardium and/or white blood cell infiltration/inflammation of the myocardium were noted on microscopic examination of the hearts.

1.3 CLINICAL EXPERIENCE WITH ACALABRUTINIB

1.3.1 Pharmacokinetics and Pharmacodynamics of Acalabrutinib in Healthy Volunteers

Acalabrutinib has been studied in 10 clinical trials in healthy volunteers. In humans, acalabrutinib has a short pharmacokinetic (PK) half-life with a long-lasting pharmacodynamic (PD) effect due to covalent binding to BTK after oral administration.

In an FIH study in subjects with R/R CLL, acalabrutinib plasma time to maximum concentration (T_{max}) values were between 0.5 and 1.0 hour for all dose cohorts (2.5 mg twice per day [BID] to 100 mg once per day [QD]), and the mean half-life ranged from 0.97 to 2.1 hours. Acalabrutinib has an absolute oral bioavailability of 25%, is best taken with water, can be taken with or without food, and does not accumulate in plasma upon repeat-dose administration. In healthy subjects, exposure was generally linear over the dose range of 15 mg to 100 mg and slightly greater than proportional between 100 mg and 400 mg. Variability in exposure to acalabrutinib is mainly due to a combination of pH-dependent absorption, and predominantly CYP3A-mediated metabolism.

For more detailed information on acalabrutinib clinical pharmacology studies, please refer to the Acalabrutinib Investigator Brochure.

1.3.2 Clinical Experience with Acalabrutinib

The Sponsor is developing acalabrutinib for the treatment of patients with cancer or autoimmune disorders. Acalabrutinib has an acceptable safety profile in clinical studies. Acalabrutinib has been administered to subjects with hematologic malignancies, solid tumors, or rheumatoid arthritis, and healthy volunteers or noncancer patients with mild- to moderate-hepatic impairment. Acalabrutinib monotherapy has also demonstrated clinical activity in patients with CLL (Awan et al. 2016), mantle cell lymphoma (MCL; Awan et al. 2016, Hillmen et al. 2016, Wang 2018; CALQUENCE® package insert), FL, and DLBCL (Dyer et al. 2018, Fowler et al.

2018).

For more detailed information on acalabrutinib clinical experience, refer to the Acalabrutinib Investigator Brochure.

Acalabrutinib, under the tradename CALQUENCE® has been approved in capsule formulation (NDA 210259) in the United States and other markets for the treatment of adult patients with MCL who have received at least one prior therapy, CLL, and small lymphocytic lymphoma (SLL). A new film-coated acalabrutinib maleate tablet formulation (NDA 216387) was first approved in the United States for the treatment of adult patients with MCL who have received at least 1 prior therapy, CLL, and SLL; acalabrutinib tablets and acalabrutinib capsules are bioequivalent.

1.4 RITUXIMAB IN LYMPHOID CANCERS

Rituximab, an anti-CD20 monoclonal antibody, is indicated for treatment of $CD20^+$ NHL as a single agent and in combination with chemotherapy. In a multicenter, open-label, single-arm study conducted in 166 patients with R/R, low-grade or follicular, B-cell NHL who received 375 mg/m^2 of rituximab intravenously weekly for 4 doses (Rituxan/MabThera package insert), the ORR was 48% with a CR rate of 6% and a median duration of response (DOR) of 11.2 months (range 1.9 to 42.1+ months). The median time to onset of response was 50 days, and disease-related signs and symptoms (including B symptoms) resolved in 64% (25/39) of those patients with such symptoms at study entry. The most common adverse reactions reported in ≥25% of subjects with R/R, low grade or follicular NHL were infusion reactions, fever (53%), lymphopenia (48% overall, 40% Grade 3 and Grade 4), chills (33%), infections (31%), and asthenia (26%) (Rituxan/MabThera package insert). Moreover, for untreated DLBCL patients studied in several large randomized studies in combination with anthracycline-based chemotherapy, patients received 375 mg/m^2 of rituximab on Day 1 of each cycle of chemotherapy up to 8 infusions.

The CR was significantly higher in the R-chemotherapy group than the group that received chemotherapy. With a median follow-up of 2 years or more, OS times were significantly higher in the R-chemotherapy group with the most common adverse reactions in ≥25% observed were infusion reactions, fever, lymphopenia, chills, infection, and asthenia in clinical trials of patients with NHL (Rituxan/MabThera package insert).

1.5 RITUXIMAB COMBINATION THERAPY IN LYMPHOID CANCERS

The combination of rituximab with a BTK inhibitor such as ibrutinib is a promising approach that is currently being evaluated in a number of lymphoid cancers, including a Phase 2, single-arm clinical trial of ibrutinib/rituximab in subjects with previously untreated FL (NCT01980654) and a comparison of ibrutinib versus ibrutinib/rituximab in subjects with relapsed CLL (NCT02007044). A completed Phase 2 study of rituximab plus ibrutinib in 40 subjects with high-risk CLL (Burger et al. 2014) found the combination was well tolerated and induced high rates of remission. Subjects received daily ibrutinib plus rituximab weekly during Cycle 1 then once per cycle until Cycle 6. The ORR was 95%, including 8% CRs; the median DOR was 15.44 months, and at 18 months, the Kaplan-Meier estimate of PFS was 78%. Toxicity was mainly of mild to moderate severity (Grade 1 to Grade 2); AEs included diarrhea (25% of subjects), bleeding events (35%, including 2.5% Grade 3), nausea (37.5%), and fatigue (17.5%). Grade 3 infections occurred in 4 patients (10%), no Grade 4 or Grade 5 infections occurred. In MCL, preliminary data have been reported on 45 subjects in a Phase 2, single-arm trial of the combination of ibrutinib and rituximab with a median of 6.5 months of follow-up (Wang et al. 2014). The ORR to date was 87%, including CR in 38% and PR in 49%. The ORR among the 33 subjects with lower Ki-67 (<50%) was 100%, with 48% CR and 52% PR. The median DOR and PFS had not yet been reached in this trial. Overall the combination was well tolerated; there were no deaths due to therapy, and Grade 3 hematology toxicity events included single cases of neutropenia and thrombocytopenia. The most common (≥20%) Grade 1 to Grade 2 nonhematologic events regardless of relationship to study therapy include fatigue, diarrhea, myalgia, dyspnea, blurred vision, nausea, dry eye, and atrial fibrillation. The combination of rituximab and ibrutinib has been evaluated in a Phase 2 clinical trial in treatment-naive patients with FL (Fowler et al. 2016). In patients receiving concurrent treatment with ibrutinib and rituximab (n=60), the ORR was 85%, with CR rate of 35%. The 12-month PFS was reported as 87%. The drug combination appeared to be well tolerated based on the lack of new safety signals in patients treated with the combination. Moreover, the acceptable safety and efficacy results to date for rituximab and the first-generation BTK inhibitor, ibrutinib, support further evaluation of rituximab with a novel BTK inhibitor such as acalabrutinib. Safety data from Part 1 of the ACE-LY-003 trial are included in the current Acalabrutinib Investigator Brochure. These data show that the

combination of acalabrutinib and rituximab is safe and well tolerated in patients with FL. For R/R DLBCL, an open-label, nonrandomized Phase 2 study, which included 80 patients (38 ABC, 20 GCB, 17 unclassified, 5 unknown) who received ibrutinib orally daily for 4 weeks until disease progression or unacceptable toxicity, responses were observed in 25% (20/80) patients, including 12 PR and 8 CR (Wilson et al. 2015). With a median follow-up of 11.53 months, OS and PFS were 6.4 and 1.6 months, respectively. Fourteen patients (37%) with ABC DLBCL had response compared with 1 patient (5%) in the GCB cohort (p=0.0106). The median response duration was 4.83 months (range, 1.02–9.26) in the ABC arm. ORR in the ABC group included a CR rate of 16% (n=6). Three patients experienced a CR in the ABC arm had ongoing responses. ORR was 22%. At a median follow-up of 10.1 and 17 months, PFS was 2 months in the ABC arm versus 1.3 months in the GCB arm (p=0.004). Median OS was 10.3 months versus 3.35 months, respectively (p=0.056).

Given the activity of ibrutinib in the ABC subtype of DLBCL (Wilson et al. 2015), a trial of R-CHOP with or without ibrutinib is in process (NCT01855750) for untreated DLBCL patients. Based on the activity of acalabrutinib in R/R DLBCL (Dyer et al. 2018), acalabrutinib will be studied in combination with rituximab and lenalidomide in R/R non-GCB DLBCL.

1.6 LENALIDOMIDE IN LYMPHOID CANCERS

Lenalidomide is an immunomodulatory agent with anti-inflammatory and antiangiogenic properties. In combination with rituximab, lenalidomide has shown promising activity in patients with FL and R/R DLBCL (Wang et al. 2013, Leonard et al. 2015). In patients with recurrent FL, at a median follow-up of 2.5 years, the ORR was 76%, the CR rate was 39%, and the median time to progression was 2 years (Leonard et al. 2015). Patients with R/R DLBCL, FL, and transformed lymphoma were evaluated in a Phase 2 clinical trial that utilized a lenalidomide-rituximab combination regimen. In this trial, the ORR was 33%, median PFS was 3.7 months, and the median OS was 10.7 months (Wang et al. 2013).

These data support the use of the lenalidomide-rituximab combination in patients with R/R FL and R/R DLBCL.

1.7 BENEFIT/RISK

Acalabrutinib is a potent, orally administered, small-molecule inhibitor of BTK. In Study ACE-CL-001, a study of acalabrutinib in subjects with CLL, including R/R or

previously untreated CLL or Richter's syndrome, no dose-limiting toxicities (DLTs) have been reported at dosages of ≤400 mg QD or 100 mg and 200 mg BID. Moreover, acalabrutinib has shown activity in other NHL histologies, including DLBCL (Dyer et al. 2018). For more detailed information on acalabrutinib clinical experience (safety and efficacy), refer to the current Acalabrutinib Investigator Brochure.

Rituximab is a well-established treatment for NHL and has been shown to be well tolerated and effective in combination with another BTK inhibitor, ibrutinib, in patients with lymphoma (Burger et al. 2014; Wang et al. 2014). In both the treatment-naive and R/R setting, rituximab is being given to patients with $CD20^+$ NHL. Based on the robust results of acalabrutinib monotherapy in subjects with CLL, MCL, FL, and DLBCL and rituximab in NHL, the evaluation of the combination of acalabrutinib and rituximab in this study is warranted in these subjects.

In an effort to improve clinical benefit, the addition of ibrutinib to the lenalidomide and rituximab regimen has been explored in recent clinical trials. This triplet regimen was evaluated in the frontline treatment of FL (Ujjani et al. 2016), and results showed this triplet regimen was not superior in efficacy than the lenalidomide-rituximab doublet regimen. There was a high incidence of rash (all grades 82%) compared with studies of the lenalidomide-rituximab doublet in a similar patient population (Ujjani et al. 2016), although rash was not a DLT in this study. Of note, patients received 90% of the expected dose intensity of rituximab, 93% of ibrutinib, and only 64% of lenalidomide (Ujjani et al. 2016). There are ongoing trials evaluating the triplet combination in R/R DLBCL (NCT02077166). These studies support the exploration of acalabrutinib in combination with lenalidomide and rituximab in R/R FL and DLBCL.

1.8 SUMMARY AND CONCLUSIONS

The purpose of Parts 1 and 2 in this study is to evaluate the safety, pharmacokinetics (Part 1), pharmacodynamics, and activity of acalabrutinib alone or in combination with rituximab in subjects with FL or MZL.

The purpose of Part 3 of this study is to evaluate the safety, activity, pharmacokinetics, and pharmacodynamics of acalabrutinib in combination with rituximab and lenalidomide in subjects with R/R FL.

The design and conduct of this study is supported by an understanding of the natural history and current therapies for subjects with B-cell NHL; knowledge of the efficacy and safety of the first-generation BTK inhibitor (e.g., ibrutinib) alone or in combination

with rituximab or rituximab and lenalidomide, in subjects with hematologic cancers, and the available nonclinical and clinical information regarding acalabrutinib.

2 STUDY OBJECTIVES

2.1 PART 1

2.1.1 Primary Objective

- To characterize the safety profile of acalabrutinib alone or in combination with rituximab in subjects with R/R FL

2.1.2 Secondary Objectives:

- To characterize the safety profile of acalabrutinib in combination with rituximab in subjects with previously untreated FL
- To characterize the PK profile of acalabrutinib alone or in combination with rituximab
- To evaluate the PD effects of acalabrutinib alone or in combination with rituximab
- To evaluate the activity of acalabrutinib alone or in combination with rituximab as measured by ORR, DOR, time-to-next treatment, and PFS

2.2 PART 2

Please note that enrollment for Part 2, Cohort 2 (R/R MZL: Acalabrutinib + Rituximab) of this study is closed.

2.2.1 Primary Objective

- To characterize the activity of acalabrutinib alone or in combination with rituximab in subjects with R/R MZL, as measured by ORR

2.2.2 Secondary Objectives

- To characterize the safety of acalabrutinib alone or in combination with rituximab in subjects with R/R MZL
- To evaluate the activity of acalabrutinib alone or in combination with rituximab in subjects with R/R MZL, as measured by DOR, PFS, and OS

2.2.3 Exploratory Objectives

- [redacted]

- [redacted]

2.3 PART 3

2.3.1 Primary Objective

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

2.3.2 Secondary Objectives:

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

2.3.3 Exploratory Objectives:

- [redacted]

3 STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This study will be conducted in 3 parts. Note: Text throughout the protocol applies to all parts of the study unless otherwise specified. At the time of Amendment 6, the sponsor made the decision to close Part 4 of the study (R/R DLBCL: Acalabrutinib + rituximab and lenalidomide).

Part 1

This part of the study is a Phase 1b, multicenter, open-label, randomized, parallel group study to be conducted at approximately 11 centers. Two cohorts will be

enrolled in parallel: The Relapsed/Refractory Cohort will include approximately 24 subjects with R/R FL, and the Treatment-Naive Cohort will include 12 subjects who have not previously been treated for FL. Note: At the time of Amendment 4, enrollment in Part 1 has been completed.

Arm 1: Acalabrutinib 100 mg by mouth (PO) BID administered approximately 12 hours apart (BID dosing=200 mg total daily dose) for 28 days

Arm 2: Acalabrutinib 100 mg PO BID administered approximately 12 hours apart (BID dosing=200 mg total daily dose) for 28 days, plus rituximab 375 mg/m^2 intravenous (IV) on Days 1, 8, 15, and 22 of Cycle 1 and Day 1 of Cycles 2 through 6

Treatment-Naive Cohort: A total of 12 subjects will receive the combination of acalabrutinib and rituximab: acalabrutinib 100 mg PO BID administered approximately 12 hours apart (BID dosing=200 mg total daily dose) for 28 days, plus rituximab 375 mg/m^2 IV on Days 1, 8, 15, and 22 of Cycle 1 and Day 1 of Cycles 2 through 6.

PK/PD testing will be performed in Cycle 1 and Cycle 2. Tumor assessments will be performed at 8- to 24-week intervals during the trial. Refer to Appendix 4 for a comprehensive list of study assessments and their timing.

Part 2

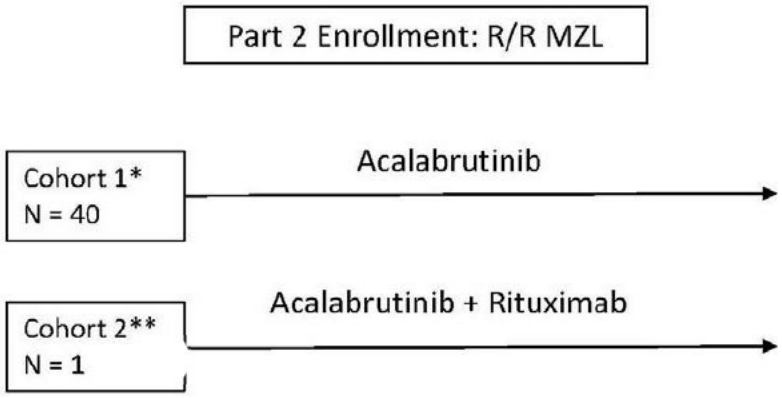
This part of the study is a Phase 2, multicenter, open-label, study to be conducted at approximately 38 centers. Up to 40 subjects with R/R MZL will be enrolled. Each cycle is 28 days. At the time of Amendment 6, the decision was made to close Cohort 2.

Cohort 1: Acalabrutinib 100 mg PO BID administered approximately 12 hours apart (BID dosing=200 mg total daily dose) for 28 days

Cohort 2: Acalabrutinib 100 mg PO BID administered approximately 12 hours apart (BID dosing=200 mg total daily dose) for 28 days, plus rituximab 375 mg/m^2 IV on Days 1, 8, 15, and 22 of Cycle 1 and Day 1 of Cycles 2 through 6.

The study schema for Part 2 of the study is presented in Figure 1.

Figure 1 Part 2 Study Schema



MZL=marginal zone lymphoma; R/R=relapsed or refractory.
* Cohort 1 enrolling up to 40 subjects.
** Cohort 2 closed for further enrollment.

Samples for PD and molecular profiling will be collected according to sampling times in the Schedule of Assessments (Appendix 5). Tumor assessments will be performed at 12-week intervals in the first year and every 24 weeks thereafter during the study.

Refer to Appendix 5 for a comprehensive list of study assessments and their timing.

Part 3

This is a dose-finding, Phase 1b, multicenter, open-label study to be conducted at approximately 38 centers. Approximately 26 to 32 subjects with R/R FL will be enrolled and treated with acalabrutinib, rituximab, and lenalidomide (each cycle is 28 days). Once a safe and tolerable dose of lenalidomide has been established, 14 subjects (as part of the 26 to 32 subjects total) will be treated on the 3 drugs at that dose of lenalidomide.

- Acalabrutinib 100 mg PO BID administered approximately 12 hours apart (BID dosing=200 mg total daily dose), until disease progression or an unacceptable toxicity occurs.
- Rituximab 375 mg/m^2 IV administered on Days 1, 8, 15, and 22 of Cycle 1, and Day 1 of every cycle starting at Cycle 2 through Cycle 6, followed by 10 additional doses of maintenance rituximab every other cycle beginning with Cycle 8 for subjects who have not progressed.
- Lenalidomide will start at 15 mg PO QD for the first 6 subjects in Cycle 1. Doses up to 20 mg PO QD will be explored. Lenalidomide will be

administered on Days 1 through 21 of a 28-day cycle.

The study schematic for Part 3 is presented in Figure 2.

Figure 2 Study Schematic for Part 3

Cycle	1	2	3	4	5	6	8	10	12	14	16	18	20	22	24	26
Acalabrutinib 100 mg PO BID	Until progression or intolerance →															
Rituximab 375 mg/m^2 IV	Induction regimen									Maintenance regimen						
	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lenalidomide[b] PO D1-21/28d	X	X	X	X	X	X	X	X	X							

BID=twice daily; D=day; DLT=dose-limiting toxicity; IV=intravenous; PO=by os (mouth); QD=once a day.

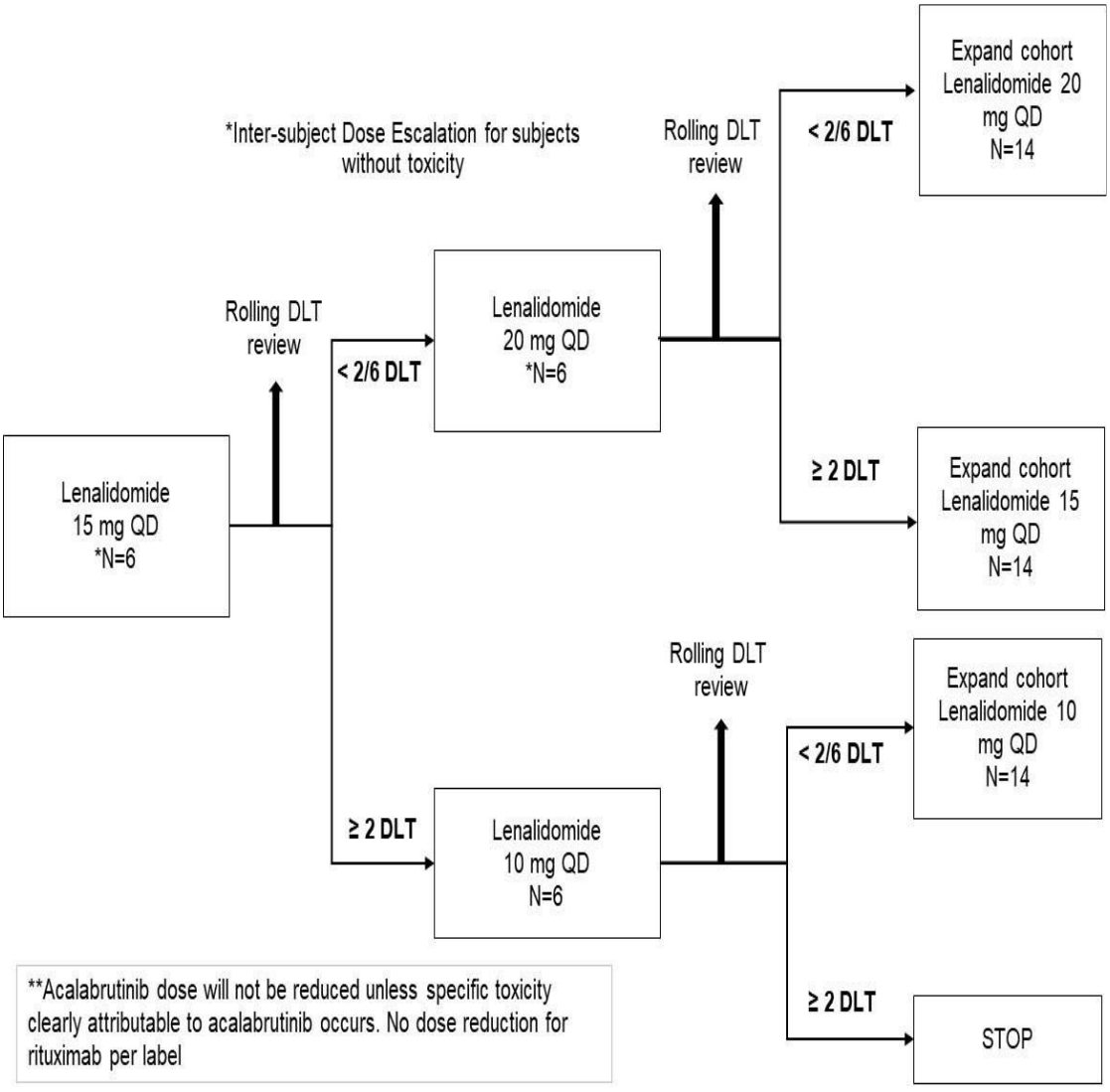
a. Rituximab will be administered weekly on Day 1 during Cycle 1 and Day 1 of every cycle from Cycles 2 through 6. Subjects who have not progressed will receive maintenance rituximab every other cycle starting on Cycle 8 for 10 additional doses until disease progression or intolerance. Lenalidomide is to be taken daily on Days 1 through 21 of each cycle.

b. The starting dose of lenalidomide is 15 mg QD and the final dose for the expansion portion of the study will be determined based on the outcome of the DLT review. Subjects will receive lenalidomide at the assigned dose or the final dose for up to 12 cycles or until disease progression or intolerance, whichever comes first.

Acalabrutinib has been used in combination with rituximab at the doses mentioned above and this combination has an acceptable safety profile (current version of Acalabrutinib Investigator Brochure). There will be an inter-subject dose escalation or de-escalation during the DLT review period to find the appropriate dose of lenalidomide that can be used in combination with acalabrutinib and rituximab.

DLT review and enrollment are presented in Figure 3 and will be conducted as follows (DLT criteria are defined in Section 3.5.5):

Figure 3 Dose-Limiting Toxicity Review and Enrollment for Part 3



DLT=dose-limiting toxicity; QD=once per day.

Six subjects are planned to be enrolled initially and treated with acalabrutinib, rituximab, and lenalidomide (15 mg PO QD) in Cycle 1. At the end of the cycle, subjects will be evaluated for DLTs on a rolling basis (Figure 3).

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

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

Refer to Appendix 6 for a comprehensive list of study assessments and their timing.

Part 4

At the time of Amendment 6, the sponsor made the decision to close Part 4 cohort to enrollment. Therefore, Part 4 has been removed.

All Parts

Twenty-eight days of study drug administration is 1 cycle. Treatment with acalabrutinib may be continued until confirmed disease progression or an unacceptable drug-related toxicity occurs.

Dose modification provisions are provided in Section 3.5.7. Note: Temporary withholding of acalabrutinib for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. All subjects who discontinue study drug

will have a safety follow-up visit 30 (+7) days after the last dose of study drug until the final data cut-off regardless of whether the subject receives a new anticancer therapy or demonstrates disease progression within this timeframe.

All subjects will have hematology, serum chemistry, hepatitis serology, and urinalysis safety panels performed at screening. For Part 1 and Part 2, once dosing commences (Day 1), all subjects will be evaluated for safety, including hematology and serum chemistry, once weekly for the first 4 weeks, every 2 weeks in Cycle 2, monthly through Cycle 13, and then every 3 months thereafter. For Part 3, once dosing commences (Day 1), all subjects will be evaluated for safety, including hematology and serum chemistry, once weekly for the first 4 weeks, every 2 weeks in Cycle 2, and monthly through Cycle 13, and for Part 3, every 8 weeks starting Cycle 14 up to Cycle 28 (rituximab infusion ends at Cycle 26) and every 3 months thereafter.

Part 3

Pregnancy testing will be performed at baseline, weekly for the first month, and then monthly for all females of childbearing potential receiving lenalidomide until 4 weeks after the last dose of lenalidomide. In addition, women of childbearing potential must use highly effective forms of contraception or abstain from sex during lenalidomide treatment and for 4 weeks after completion of lenalidomide treatment.

All subjects (males and females) receiving lenalidomide must be enrolled in the REVLIMID Risk Evaluation and Mitigation Strategy (REMS) program.

3.1.1 Efficacy Parameters

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

Part 1

- ORR
- DOR
- PFS
- Time-to-next treatment

Part 2 and Part 3

- ORR
- DOR
- PFS
- OS

3.1.2 Safety Parameters

The safety of acalabrutinib alone or in combination with rituximab or rituximab and lenalidomide will be characterized by the type, frequency, severity, timing of onset, duration, and relationship to study drug of any AEs; serious adverse events (SAEs); or AEs leading to study treatment delay, dose modification, or discontinuation.

For consistency of interpretation, AEs will be coded using MedDRA, and the severity of AEs and laboratory abnormalities will be graded using the Common Terminology Criteria for Adverse Events (CTCAE; Part 1 will use Version 4.03 and Parts 2 and 3 will use Version 5.0). Standard definitions for seriousness will be applied (see Section 6.2).

3.1.3 Pharmacokinetic, Pharmacodynamic Parameters, and Molecular Profiling

Part 1

Standard PK parameters for acalabrutinib in plasma will be evaluated in this study. A full description of the PK parameters is provided in Section 5.5.5. The occupancy of BTK by acalabrutinib will be measured in peripheral blood mononuclear cells (PBMCs) and bone marrow, when available, with the aid of an acalabrutinib analogue probe.

Part 2

No PK analysis will be performed in Part 2. The occupancy of BTK by acalabrutinib will be measured in PBMCs and bone marrow, when available, with the aid of an acalabrutinib analogue probe. [redacted]

Part 3

Sparse acalabrutinib PK samples will be collected and analyzed to investigate the relationship between acalabrutinib and its active metabolite (ACP-5862) concentration and response. The occupancy of BTK by acalabrutinib will be measured in PBMCs and bone marrow, when available, with the aid of an acalabrutinib analogue probe. [redacted]

[redacted]

3.2 END OF STUDY

The final data cut-off to support final database lock will be based on the projected median follow-up of approximately 30 months for subjects in Part 2 which is projected to occur approximately 23 months after last subject first dose, this is estimated to be approximately 25 August 2023. A median follow-up of approximately 30 months is deemed adequate follow-up for the FL and MZL population in this study. In addition to the above, a final data cut to support Part 1 final database lock will occur approximately 71 months after last subject first dose in Part 1; this is expected to provide adequate long-term follow up for the FL subjects enrolled in the study.

A Clinical Study Report (CSR) will be written using the final data cut-off for Part 1 and a second CSR will be written using the final data cut-off for Parts 2 and 3.

The end of the study is defined as the final data cut-off for the final analysis.

AstraZeneca will continue to supply acalabrutinib in the continued access phase of this study and after completion of this study while, in the opinion of the investigator, the subject is benefitting.

In the event that product development reaches a point where alternative product supply options become available, then these alternative product supply options will be discussed by the Sponsor with the investigator. The Sponsor will work with the investigator to transition the subject(s) to alternative supply, where possible.

It is recommended that investigators continue to observe ongoing subjects at the frequency employed prior to the primary DCO.

Protocol dose modification and stopping criteria are to be followed while a subject is receiving acalabrutinib. A change in the dose/schedule of acalabrutinib should only occur for safety reasons, based on the investigator's judgement, and should generally follow the approach for dose reduction and discontinuation as described in this protocol.

After the final DCO, the clinical database will close to new data, however SAEs must continue to be reported. Subjects may be withdrawn from the study at this time; however, they may remain on study treatment beyond closure of the database if, in the opinion of the Investigator, the subject continues to receive benefit from study treatment. Any subject who is eligible to continue receive acalabrutinib after database closure is considered to have completed the study when he/she meets one of the discontinuation

criteria listed in Section 3.8.

Dispensation and reconciliation of the investigational product will be handled by the study site at each subject's visit. The investigational product accountability information must be collected until all subjects have completed treatment.

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

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

Food and Drug Administration requirements defines two completion dates:

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

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

3.3 RATIONALE FOR STUDY DESIGN AND DOSING REGIMEN

As described in Section 1.7, data from an FIH study (ACE-CL-001) in subjects with R/R CLL have shown that acalabrutinib is well tolerated at dosages from 100 mg to 400 mg QD or 100 mg to 200 mg BID. In addition, data from ACE-CL-001 showed that BTK occupancy with acalabrutinib in peripheral blood is >95% at 4 hours after QD dosing but decreases to <95% at 24 hours with QD dosing; whereas, with BID dosing, complete BTK occupancy (95% to 99%) is maintained over 24 hours at steady state (Byrd et al. 2016). These data suggest that de novo synthesis of BTK can occur within 24 hours in peripheral blood cells. BID dosing may ensure BTK inhibition for the entire 24 hours, which may be beneficial in terms of increased efficacy and/or decreased development of resistance to acalabrutinib.

Rituximab is indicated for subjects with a variety of $CD20^+$ NHLs as a single agent and in combination with chemotherapy. The Rituxan/MabThera package insert recommends a dose of 375 mg/m^2 given weekly for 4 or 8 weeks in R/R FL with optional extended

dosing. The weekly dosing regimen has been studied in combination with the BTK inhibitor, ibrutinib, in CLL and MCL (Burger et al. 2014, Wang et al. 2014). In both untreated and R/R FL, ongoing Phase 3 clinical trials of rituximab and lenalidomide are utilizing a regimen of 375 mg/m^2 rituximab weekly for the first 4 weeks (Cycle 1) and then once per cycle for the next 4 to 5 cycles (NCT01476787, NCT01650701, NCT01938001). Therefore, Part 1 of this study has been designed to evaluate the safety, pharmacokinetics, pharmacodynamics, and activity of acalabrutinib alone or in combination with rituximab in subjects with R/R FL; Part 2 has been designed to evaluate the activity, safety, and pharmacodynamics of acalabrutinib alone or in combination with rituximab in subjects with R/R MZL. The dosing regimen will be 100 mg acalabrutinib BID administered orally and 375 mg/m^2 rituximab weekly administered intravenously for the first 4 weeks (Cycle 1) and then once per cycle for the next 5 cycles for both Part 1 and Part 2 of the study.

In Part 3 of the study, the rituximab regimen will be administered at 375 mg/m^2 IV weekly for the first 4 weeks in Cycle 1, then on Day 1 of every cycle from Cycles 2 through 6, followed by maintenance rituximab every other cycle beginning with Cycle 8 for subjects who have not progressed.

Lenalidomide is indicated for subjects with multiple myeloma, myelodysplastic syndrome (MDS) with deletion 5q, and MCL (Revlimid package insert). The monotherapy dose ranges from 10 mg for MDS to 25 mg for MM and MCL. In the study combining lenalidomide with rituximab for R/R FL, lenalidomide was started at 15 mg in Cycle 1 and then escalated to 20 mg in Cycles 2 through 12 for 21 of 28 days with an ORR of 76% in combination with rituximab compared with 53% for lenalidomide alone (Leonard et al. 2015). In untreated patients with FL, ibrutinib was added to lenalidomide and rituximab. Similarly, the starting dose of lenalidomide was 15 mg with dose escalated to 20 mg for 21 of 28 days with rituximab and ibrutinib. The combination was not more efficacious than rituximab-lenalidomide. There were no protocol-defined DLTs; however, increased toxicity (rash 82%, diarrhea 64%, and fatigue 59%) and dose modifications were required in this untreated FL group, so a subsequent study is not planned. Of note, in patients with previously untreated FL receiving ibrutinib in combination with rituximab and lenalidomide, patients received 90% of the expected dose intensity of rituximab, 93% of ibrutinib, and only 64% of lenalidomide (Ujjani et al. 2016). Given this experience, Part 3 of this study will start with 15 mg of lenalidomide to be combined with acalabrutinib and rituximab. For Part 3, lenalidomide will be given on Days 1 through 21 of a 28-day cycle up to 12 cycles or until disease progression or an unacceptable toxicity

occurs, whichever comes first.

3.4 SELECTION OF STUDY POPULATION

3.4.1 Inclusion Criteria Part 1

Eligible subjects will be considered for inclusion in this study if they meet **all** of the following criteria:

1. Men and women ≥18 years of age.
2. Relapsed/Refractory Cohort: A confirmed diagnosis of FL Grade 1, 2, or 3a that has relapsed after, or been refractory to ≥1 prior therapy for FL and which requires treatment per National Cancer Institute or International Working Group guidelines. Documented failure to achieve at least PR with, or documented disease progression after, the most recent treatment regimen.

   Treatment-naive Cohort: A confirmed diagnosis of FL Grade 1, 2, or 3a that requires treatment per National Cancer Institute or International Working Group guidelines in subjects who have not previously received systemic anticancer therapy for FL.
3. Presence of radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (defined as the presence of ≥1 lesion that measures ≥2.0 cm in the longest dimension and ≥1.0 cm in the longest perpendicular dimension as assessed by computed tomography [CT] scan).
4. ECOG performance status of ≤2.
5. Agreement of women of childbearing potential (WOCBP) to use highly effective methods of contraception during the study and for 2 days after the last dose of acalabrutinib or 3 months after the last dose of rituximab, whichever is longer, if sexually active and able to bear or beget children. Highly effective forms of contraception are defined in Section 3.7.6.
6. Men must agree to refrain from sperm donation during the study and for 3 months after the last dose of rituximab.
7. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules or tablets without difficulty.
8. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local patient privacy regulations).

3.4.2 Exclusion Criteria Part 1

Subjects will be ineligible for this study if they meet **any** of the following criteria:

1. Prior malignancy (other than indolent B-cell NHL), except for adequately treated basal cell or squamous cell skin cancer, in situ cancer, or other cancer from which the subject has been disease free for ≥2 years.
2. Known CNS lymphoma or leptomeningeal disease.
3. A life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of acalabrutinib, or put the study outcomes at undue risk.
4. Known history of a bleeding diathesis (e.g., hemophilia, von Willebrand disease).
5. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or corrected QT interval (QTc) >480 msec.
6. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, gastric bypass, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.
7. Any immunotherapy within 4 weeks of first dose of study drug.
8. Relapsed/Refractory Cohort: The time from the last dose of the most recent chemotherapy or experimental therapy to the first dose of study drug is <5 times the half-life of the previously administered agent(s).
9. Prior exposure to a BCR inhibitor (e.g., BTK, phosphonositide-3 kinase [PI3K], or spleen tyrosine kinase [SYK] inhibitors) or BCL-2 inhibitor (e.g., venetoclax).
10. Known history of anaphylaxis or hypersensitivity to rituximab (Rituxan/MabThera) or any of its components.
11. Ongoing immunosuppressive therapy, including systemic or enteric corticosteroids for treatment of FL or other conditions. Note: Subjects may use topical or inhaled corticosteroids or low-dose steroids (≤20 mg of prednisone or equivalent) as therapy for comorbid conditions. During study participation, subjects may also receive systemic or enteric corticosteroids as needed for treatment-emergent comorbid conditions.
12. Grade ≥2 toxicity (other than alopecia) continuing from prior anticancer therapy including radiation.
13. Known history of HIV or active infection with hepatitis C virus (HCV) or any uncontrolled active systemic infection.

14. Known hepatitis B infection or positive for hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (anti-HBc). Since intravenous immunoglobulins (IVIG) may cause false positive hepatitis serology, subjects who are receiving prophylactic IVIG and have positive HBsAg or anti-HBc must have negative hepatitis B DNA to be eligible.
15. Major surgery within 4 weeks before first dose of acalabrutinib.
16. Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenia purpura.
17. History of stroke or intracranial hemorrhage within 6 months before the first dose of acalabrutinib.
18. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonist (e.g., phenprocoumon) within 7 days of first dose of study drug.
19. Requires treatment with proton-pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). Note: this criterion no longer applies to subjects who have switched from acalabrutinib capsules to tablets.
20. Received a live virus vaccination within 28 days of first dose of study drug.
21. ANC $<0.75 \times 10^9$/L or platelet count $<50 \times 10^9$/L. For subjects with documented disease involvement in the bone marrow, ANC $<0.50 \times 10^9$/L or platelet count $<30 \times 10^9$/L.
22. Creatinine >2.5 × institutional upper limit of normal (ULN); total bilirubin >2.5 × ULN; and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3.0 × ULN.
23. Breastfeeding or pregnant.
24. Concurrent participation in another therapeutic clinical trial.
25. Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before screening.

3.4.3 Inclusion Criteria Part 2

Eligible subjects will be considered for inclusion in this study if they meet **all** of the following criteria:

1. Men and women ≥18 years of age.
2. Histologically confirmed MZL including splenic, nodal, and extranodal sub-types
    a. Subjects with splenic MZL must have an additional measurable lesion, nodal or extranodal, as described in inclusion criterion #4;

   b. Subjects with gastric MALT lymphoma must be H. pylori-negative (including subjects after successful elimination of H. pylori) or refractory to H. pylori-eradication therapy by a minimum time of 12 months by a pathology confirmation or by a ^{13}C urea test (proton-pump inhibitors and H2 blockers should be discontinued or withheld for at least 14 days and 7 days, respectively, and antibiotics for treating H. pylori, such as those with anti-helicobacter action and bismuth preparations, should be withdrawn at least 30 days before H. pylori testing [Savarino et al. 1999]).

3. Previous therapy:
   a. Cohort 1: Previously received 1 or more lines of systemic therapy including at least 1 CD20-directed regimen (either as monotherapy or as chemoimmunotherapy for MZL) with documented failure to achieve at least PR, or documented disease progression after the most recent treatment regimen.
   b. Cohort 2: Previously received 1 or more lines of therapy including at least 1 prior systemic therapy for MZL **or** radiation therapy with documented failure to achieve at least PR, or document disease progression after the most recent treatment regimen.
4. Presence of radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (defined as the presence of ≥1 lesion that measures ≥2.0 cm in the longest dimension and ≥1.0 cm in the longest perpendicular dimension as assessed by CT scan). Lesions in anatomical locations, such as extremities or soft tissue lesions, that are not well visualized by CT may be measured by magnetic resonance imaging (MRI) instead; subjects with spleen-only disease are considered as not having measurable disease.
5. ECOG performance status of ≤2.
6. WOCBP must agree to use highly effective methods of contraception during the study and for 2 days after the last dose of acalabrutinib or 12 months after the last dose of rituximab, whichever is longer, if sexually active and able to bear or beget children. Highly effective methods of contraception are defined in Section 3.7.6.
7. Men must agree to refrain from sperm donation during the study and for 3 months after the last dose of rituximab.
8. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules or tablets without difficulty.
9. Ability to understand the purpose and risks of the study and provide signed and

dated informed consent and authorization to use protected health information (in accordance with national patient privacy regulations).

3.4.4 Exclusion Criteria Part 2

Subjects will be ineligible for this study if they meet **any** of the following criteria:

1. Prior malignancy (other than indolent B-cell NHL), except for adequately treated basal cell or squamous cell skin cancer, in situ cancer, or other cancer from which the subject has been disease free for ≥2 years.
2. Known medically apparent CNS lymphoma or leptomeningeal disease.
3. Known evidence of transformation to another aggressive lymphoma.
4. A life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of acalabrutinib, or put the study outcomes at undue risk.
5. Known history of a bleeding diathesis (e.g., hemophilia, von Willebrand disease).
6. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or corrected QT interval using Fridericia formula (QTcF) >480 msec.
7. Malabsorption syndrome, disease significantly affecting gastrointestinal function (excluding gastric MALT), or resection of the stomach or small bowel, gastric bypass, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.
8. This criterion was removed under Amendment 5.
9. This criterion was removed under Amendment 5.
10. Prior exposure to a BCR inhibitor (e.g., BTK, or SYK inhibitors).
11. For Cohort 2, evidence of $CD20^-$ MZL and/or known history of anaphylaxis or hypersensitivity to rituximab (Rituxan/MabThera) or any of its components.
12. Ongoing immunosuppressive therapy, including systemic or enteric corticosteroids for treatment or other conditions within 1 week before the first dose of study drug. Note: Subjects may use topical or inhaled corticosteroids or low-dose steroids (≤20 mg of prednisone or equivalent for up to 2 weeks) as therapy for comorbid conditions. However, subjects requiring systemic steroids at daily doses >20 mg prednisone equivalent of systemic exposure are not allowed.
13. Grade ≥2 toxicity (other than alopecia or laboratory value requirements mentioned in

Part 2) continuing from prior anticancer therapy including radiation.

14. Uncontrolled active systemic fungal, bacterial, viral, or other infection (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment), or intravenous anti-infective treatment within 2 weeks before first dose of study drug.
15. Known history of infection with HIV.
16. Serologic status reflecting active hepatitis B or C infection.
    a. Subjects who are anti-HBc positive and who are surface antigen negative will need to have a negative hepatitis B virus (HBV) DNA polymerase chain reaction (PCR) result before enrollment. Subjects who are HBsAg positive or hepatitis B PCR positive will be excluded.
    b. Subjects who are anti-HCV positive will need to have a negative PCR result before enrollment. Subjects who are hepatitis C PCR positive will be excluded.
17. History of allogeneic stem cell (or organ) transplantation.
18. This criterion was removed under Amendment 5.
19. Major surgery within 4 weeks before first dose of acalabrutinib.
20. Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenia purpura.
21. History of stroke or intracranial hemorrhage within 6 months before the first dose of acalabrutinib.
22. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonist (e.g., phenprocoumon) within 7 days of first dose of study drug.
23. Requires treatment with proton-pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). Note: this criterion no longer applies to subjects who have switched from acalabrutinib capsules to tablets.
24. Received a live virus vaccination within 28 days of first dose of study drug.
25. ANC $<1.0 \times 10^9$/L or platelet count $<100 \times 10^9$/L. For subjects with documented disease involvement in the bone marrow, ANC $<0.50 \times 10^9$/L or platelet count $<30 \times 10^9$/L.
26. Creatinine >1.5 × institutional ULN; total bilirubin >1.5 × ULN; and AST or ALT >2.5 × ULN.
27. Breastfeeding or pregnant.
28. Concurrent participation in another therapeutic clinical trial.

29. In the absence of gastric MALT (subject to inclusion criterion 2b) presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before screening or diagnosed >3 months before screening and without confirmed resolution by endoscopy.
30. Received any chemotherapy, external beam radiation therapy, anticancer antibodies, or investigational drug within 30 days before first dose of study drug.
31. History of or ongoing progressive multifocal leukoencephalopathy (PML).

3.4.5 Inclusion Criteria Part 3

Eligible subjects will be considered for inclusion in this study if they meet **all** of the following criteria.

1. Men and women ≥18 years of age.
2. For subjects with FL: Pathologically confirmed diagnosis of FL Grade 1, 2, or 3a that has relapsed after, or been refractory to, ≥1 prior therapy for FL and which requires treatment per National Cancer Institute or European Society for Medical Oncology (ESMO) clinical practice guidelines.
3. This criterion was removed under Amendment 6.
4. Subjects must have previously received at least 1 frontline standard chemoimmunotherapy regimen.
5. Subjects with suspected residual disease after the treatment regimen directly preceding study enrollment must have biopsy-demonstrated residual FL.
6. Documented R/R disease, defined as either: 1) recurrence of disease after a CR or PR, or 2) stable disease or progressive disease at completion of the treatment regimen preceding entry to the study (residual disease).
7. Presence of radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (defined as the presence of ≥1 lesion that measures ≥2.0 cm in the longest dimension and ≥1.0 cm in the longest perpendicular dimension as assessed by CT scan).
8. ECOG performance status of ≤2.
9. Females of reproductive potential must
    a. have 2 negative pregnancy tests prior to initiating treatment with lenalidomide. The first should be within 10 to 14 days and the second test within 24 hours prior to first dose of lenalidomide.
    b. commit to abstain continuously from heterosexual sex or use highly effective

methods of contraception. Contraception must be used beginning 4 weeks prior to initiating treatment with lenalidomide, during therapy with any study drug, and during dose interruptions for lenalidomide. Contraception must be used for 2 days after the last dose of acalabrutinib,12 months after the last dose of rituximab, or 4 weeks after the last dose of lenalidomide, whichever is later.

10. Men must agree to use a synthetic or latex condom during any sexual contact with female of reproductive potential or with a pregnant partner while taking lenalidomide and for up to 4 weeks after last dose of lenalidomide, even if they have undergone a successful vasectomy since lenalidomide is present in the semen. Men must agree to refrain from sperm donation during the study and for 3 months after the last dose of rituximab or 4 weeks after the last dose of lenalidomide, whichever is later.
11. Subjects must not donate blood during treatment with lenalidomide and for 4 weeks after discontinuation of lenalidomide.
12. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules or tablets without difficulty.
13. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national patient privacy regulations).

3.4.6 Exclusion Criteria Part 3

1. Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cancer, or other cancer from which the subject has been disease free for ≥2 years.
2. Subjects for whom the goal of therapy is tumor debulking before stem cell transplant.
3. Known history or presence of CNS lymphoma or leptomeningeal disease.
4. Transformed DLBCL or DLBCL with coexistent histologies (e.g., FL or mucosa-associated lymphoid tissue and primary mediastinal large B-cell lymphoma [PMBCL]).
5. A life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of acalabrutinib or lenalidomide, or put the study outcomes at undue risk.
6. Known history of a bleeding diathesis (e.g., hemophilia, von Willebrand disease).
7. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any

Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or QTcF >480 msec. Exception: Subjects with controlled, asymptomatic atrial fibrillation during screening are allowed to be enrolled on study.

8. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, gastric bypass, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.
9. Received any chemotherapy, external beam radiation therapy, anticancer antibodies, or investigational drug within 30 days before first dose of study drug.
10. Prior exposure to a BCR inhibitor (e.g., BTK or SYK inhibitors), lenalidomide, or CAR-T cell therapy.
11. Known history of anaphylaxis or hypersensitivity to rituximab (Rituxan/MabThera) or any of its components.
12. Subjects with a prior history of Grade 4 rash associated with thalidomide treatment.
13. Ongoing immunosuppressive therapy, including systemic (e.g., IV or oral) corticosteroids within 2 weeks before the first dose of study drug. Note: Subjects may use topical or inhaled corticosteroids or low-dose steroids (≤20 mg prednisone equivalent/day for ≤2 weeks) as a therapy for comorbid conditions. During study participation, subjects may also receive systemic (e.g., IV or oral) corticosteroids as needed for treatment-emergent comorbid conditions.
14. Grade ≥2 toxicity (other than alopecia or laboratory value requirements mentioned in Part 3 exclusion criteria) continuing from prior anticancer therapy including radiation.
15. Uncontrolled active systemic fungal, bacterial, viral, or other infection (defined as exhibiting ongoing signs or symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment), or intravenous anti-infective treatment within 2 weeks before first dose of study drug.
16. Known history of infection with HIV.
17. Serologic status reflecting active hepatitis B or C infection.
    a. Subjects who are anti-HBc positive and who are surface antigen negative will need to have a negative PCR result before enrollment. Subjects who are HBsAg positive or hepatitis B PCR positive will be excluded.
    b. Subjects who are HCV antibody (anti-HCV) positive will need to have a negative PCR result before enrollment. Subjects who are HCV PCR positive will be excluded.
18. History of allogeneic stem cell (or organ) transplantation.

19. Major surgery within 4 weeks before first dose of acalabrutinib.
20. Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenia purpura.
21. History of stroke or intracranial hemorrhage within 6 months before the first dose of acalabrutinib.
22. Requires or has received anticoagulation with warfarin or equivalent vitamin K antagonist (e.g., phenprocoumon) within 7 days of first dose of study drug.
23. Received a live virus vaccination within 28 days of first dose of study drug.
24. ANC $<1.0 \times 10^9$/L or platelet count $<75 \times 10^9$/L. Subjects will only be considered eligible if peripheral blood counts can be maintained independent of growth factors or transfusions during screening.
25. Creatinine clearance of <60 mL/min, calculated using the formula of Cockcroft and Gault [(140-Age) * Mass (kg)/(72 * creatinine mg/dL) * 0.85 if female].
26. Total bilirubin >1.5 × ULN, or AST or ALT >2.5 × ULN, unless directly attributable to Gilbert's syndrome.
27. Requires treatment with a strong CYP3a inhibitor/inducer.
28. Requires treatment with proton-pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole or pantoprazole). Subject receiving proton-pump inhibitors who switch to H2-receptor antagonists or antacids are eligible for enrollment to this study. Note: this criterion no longer applies to subjects who have switched from acalabrutinib capsules to tablets.
29. Breastfeeding or pregnant.
30. Concurrent participation in another therapeutic clinical trial.
31. History of or ongoing PML.

3.4.7 Replacement of Subjects

Part 1 and Part 2

Any subject who does not complete Cycle 2 may be replaced at the discretion of the study investigator and sponsor. Should the decision be made to replace a subject, the replacement subject will be assigned to the same treatment combination regimen as the original subject.

Part 3

Any subject who does not complete study therapy through Cycle 1 for reasons other than the occurrence of a DLT may be replaced at the discretion of the study investigator and sponsor. Should the decision be made to replace a subject, the replacement

subject will be assigned to the same treatment combination regimen as the original subject.

3.4.8 Enrollment and Procedures

Part 1

Enrollment of a subject into the study will be performed according to the following procedure:

- The study center will notify the sponsor when a clinically eligible subject is identified and is ready to screen, to ensure enrollment availability on the study.
- After the subject has signed and dated the Informed Consent Form (ICF), all screening procedures have been completed, and eligibility has been confirmed, the subject can be officially enrolled in the study.
- To enroll a subject and confirm eligibility, the study center will fax/email a completed Enrollment Confirmation Form to the sponsor. The enrollment date will be the date that the form is faxed/emailed to the sponsor.
- An Enrollment Confirmation Form will be completed and faxed/emailed to the study center by the sponsor within 24 hours.
- The Enrollment Confirmation Form will contain treatment allocation generated by the sponsor.
- The sponsor will aim to fax/email a completed Enrollment Confirmation Form to the study center within 24 hours of receipt.

Treatment must begin within the screening window (Section 4.1) and after the site has received the treatment allocation from the sponsor. Study treatment is not blinded on this study.

Part 2 and Part 3

Subjects will be enrolled in Part 2 and Part 3 according to the following procedure:

- The Sponsor's clinical team will inform all sites which part of the study is open for enrollment.
- The study center will notify and obtain an approval of the histology from the sponsor when a potential subject is identified and ready to be screened.
- After the subject has signed and dated the ICF, all screening procedures have been completed, and eligibility has been confirmed, the subject can be officially enrolled in the study.

- To enroll a subject and confirm eligibility, the study center will fax/email a completed Enrollment Confirmation Form to the sponsor. The enrollment date will be the date that the form is faxed/emailed to the sponsor.
- The sponsor will aim to fax/email a signed and completed Enrollment Confirmation Form to the study center within 24 hours of receipt.

Study treatment must begin within the screening window (Section 4.1).

3.5 STUDY DRUG

3.5.1 Premedications

No specific premedications or supporting medications are required in conjunction with acalabrutinib administration.

Prior to each rituximab infusion, subjects should be premedicated according to the Rituxan/MabThera package insert and institutional standard practices (e.g., with acetaminophen and an antihistamine). The Rituxan package insert warns that **"Rituxan administration can result in serious, including fatal infusion reactions. Deaths within 24 hours of Rituxan infusion have occurred. Approximately 80% of fatal infusion reactions occurred in association with the first infusion. Monitor patients closely. Discontinue Rituxan infusion for severe reactions and provide medical treatment for Grade 3 or 4 infusion reactions."**

Subjects receiving lenalidomide are at risk for venous and arterial thromboembolism and should receive low-dose aspirin as prophylaxis. Subjects at high risk for venous and arterial thromboembolism should receive additional prophylaxis including low molecular weight heparin, per the discretion of the investigator. High-risk subjects are those with a family history of venous thromboembolism, smoker, oral contraceptives, history of diabetes mellitus or coronary artery disease, and signs and symptoms of thromboembolism.

AEs of tumor lysis syndrome (TLS) have been observed in subjects treated with lenalidomide. Subjects at risk for TLS should be given TLS prophylaxis per institutional standard of care.

3.5.2 Formulation, Packaging, and Storage

Acalabrutinib is manufactured according to cGMP regulations and will be provided to the investigational site by the Sponsor or designee. Acalabrutinib should be stored according to the instructions on the label that is affixed to the package containing the drug product.

As of Clinical Study Protocol (CSP) Version 8.0, acalabrutinib is supplied in 2 formulations (hard gelatin capsules or orange film-coated tablets) for oral administration. Acalabrutinib capsules and tablets are bioequivalent. Each acalabrutinib capsule or tablet contains 100 mg of drug substance and standard pharmaceutical grade excipients. Acalabrutinib will be provided in white, high-density polyethylene bottles.

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

Refer to the Acalabrutinib Investigator Brochure for additional information.

Rituximab (Rituxan/MabThera) injection is a commercial product (Genentech, Inc., South San Francisco, CA/Roche, Basal Switzerland). Rituximab is available in 100 mg/10 mL single-use vials and 500 mg/50 mL single-use vials.

Lenalidomide (Revlimid®) is a commercial product (Celgene, Inc, Summit, NJ). Lenalidomide is available as capsules containing 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg of drug substance.

Refer to product information from the manufacturers for details on formulation, packaging, and storage of rituximab and lenalidomide.

3.5.3 Administration of Study Drug

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

Acalabrutinib is intended to be administered orally with 8 ounces (approximately 240 mL) of water. Acalabrutinib taken with an acidic beverage may impact exposure to acalabrutinib (refer to the current Acalabrutinib Investigator brochure). Acalabrutinib may be administered without regard to food. The capsules or tablets should be swallowed intact and subjects should not attempt to open capsules or crush tablets, and both formulations should not be dissolved in water.
Acalabrutinib should be taken BID, approximately 12 hours apart. Dietary restrictions are provided in Section 3.7.4.

If a dose is missed, it can be taken within 3 hours after the scheduled time with a return to the normal schedule with the following dose. If the time from the scheduled time of

administration has been >3 hours, the dose should not be taken, and the subject should take the next dose. The missed dose will not be made up and must be returned to the site at the next scheduled visit.

Rituximab is to be administered as an IV infusion, not an IV push or bolus. Detailed instructions for the preparation and administration of rituximab are provided in the Rituxan/MabThera package insert and per institutional standards. No dose reductions for rituximab are allowed. On days when both acalabrutinib and rituximab are administered, the rituximab infusion should begin approximately 1 hour after the acalabrutinib dose.

Subjects will continue on acalabrutinib after completion of rituximab treatment or may do so if rituximab is discontinued due to intolerability at any time in the study.

Lenalidomide is to be administered orally at approximately the same time each day, either with or without food. The capsules should be swallowed whole with water. The capsules should not be opened, broken, or chewed. Lenalidomide is administered for the first 21 days of each 28-day cycle. On days that both acalabrutinib and lenalidomide are administered, lenalidomide should be taken approximately 30 minutes prior to the first daily dose of acalabrutinib. Dose modification provisions are provided in Section 3.5.7.

3.5.4 Assuring Subject Compliance

Subjects will receive their supply of acalabrutinib in the clinic on Day 1 of Cycle 1 and Cycle 2, and Day 1 of subsequent scheduled visits. For treatments that are taken in the clinic, subjects should take acalabrutinib from the drug dispensed for them for that particular time period. All other acalabrutinib treatments will be taken at home. Subjects will receive a diary to record the specific time each dose was taken and to record reasons for any missed doses.

Subject compliance will be assessed at every visit. The subject will be instructed to bring the diary and any remaining capsules or tablets to the clinic at their next visit. The administrator will review the diary and ask the subject if all the capsules or tablets were administered. Any remaining or returned capsules and tablets will be counted and recorded as described in Section 7.11. Returned capsules and tablets must not be redispensed to another subject. The study staff will resupply the subject with the correct number of capsules or tablets needed for use until the next visit.

3.5.5 Definition of Dose-limiting Toxicity (Part 3)

A DLT will be defined as the occurrence of any of the following study drug-related AEs

during the DLT review period. (Note: AEs clearly related to disease progression or the subject's medical history and associated comorbidities considered by the investigator to be unrelated to study drugs, will not be considered DLTs. Infusion reactions clearly associated with rituximab infusion will not be considered DLTs.):

1. Non-hematologic DLTs include:

    a) Grades 3 or 4 nausea, vomiting, or diarrhea lasting >7 days despite optimal antiemetic or antidiarrhea management or any Grade 3 or Grade 4 toxicity
    b) Any grade Stevens-Johnson syndrome or toxic epidermal necrolysis
    c) AST or ALT >3 × ULN concurrently with total bilirubin >2 × ULN
    d) Clinical TLS not resolving to baseline after a 2-week treatment delay

- Exceptions are deep vein thrombosis (DVT), correctable electrolyte abnormalities, or Grade 3 or Grade 4 laboratory abnormalities lasting ≤7 days; Grades 3 or 4 fatigue, anorexia, non-neutropenic fever, Grade 3 rash resolving to Grade 2 within 10 days (allowed therapy with steroids)

2. Hematologic DLTs include:

    a) Grade 3 or Grade 4 neutropenia with fever ≥38.5°C or infection, or Grade 4 neutropenia lasting >7 days despite adequate granulocyte-colony stimulating factors (G-CSF) use
    b) Grade 3 or Grade 4 thrombocytopenia with hemorrhage. If thrombocytopenia improves to Grade ≤2 or to ≥80% of the baseline value within 28 days, without a platelet transfusion, this will not be considered a DLT
    c) Any Grade 4 hematologic toxicity unrelated to the underlying disease

3. Any study drug-related Grade 5 AE

4. Any study drug-related toxicity leading to an individual drug dose delay of >21 consecutive days for acalabrutinib or >14 consecutive days for lenalidomide will be considered as a DLT. Subjects should receive at least one dose of rituximab in Cycle 1 to be evaluable for a DLT.

3.5.6 Dose Delays

Study treatment with acalabrutinib, rituximab, lenalidomide (if applicable), or combination treatment 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 medical monitor. Study drug may be held for a maximum of 28 consecutive days from expected

dose due to toxicity. Study treatment should be discontinued in the event of a toxicity lasting >28 days, unless reviewed and approved by the medical monitor.

Note: Temporary withholding of acalabrutinib for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms.

3.5.7 Dose Modification and Discontinuation

All acalabrutinib dose modifications (Table 1 and Table 2) should be discussed with the medical monitor prior to instituting changes. For toxicities that are common to both acalabrutinib and lenalidomide, consider adjusting the dose of lenalidomide before adjusting the dose of acalabrutinib per the recommendations below:

- Grade 4 neutrophil count decreases (ANC <500/μL) for >7 days (hematopoietic colony-stimulating factors are permitted per American Society of Clinical Oncology [ASCO] guidelines] and use must be recorded on the electronic case report form [eCRF])
- Grade 3 platelet count decreases in the presence of significant bleeding
- Grade 4 platelet count decreases
- Grade 3 or 4 nausea, vomiting, or diarrhea, if persistent despite optimal antiemetic and/or antidiarrheal therapy
- Any other Grade 4 toxicity or unmanageable Grade 3 toxicity

Table 1 Drug Modification and Discontinuation Actions for Acalabrutinib (in Combination with Lenalidomide)

Occurrence	Action
1st–2nd	Hold acalabrutinib until recovery to Grade ≤2 or baseline; may restart at original dose level (100 mg BID)
3rd	Hold acalabrutinib until recovery to Grade ≤2 or baseline; restart at 100 mg once daily
4th	Discontinue acalabrutinib

BID=twice daily.

Table 2 Drug Modification and Discontinuation Actions for Acalabrutinib (Without

Lenalidomide)

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 100 mg once daily
4th	Discontinue acalabrutinib

BID=twice daily.

Whenever possible, any dose adjustment of acalabrutinib should be discussed between the investigator and the Sponsor's medical monitor 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 on the appropriate eCRF.

Rituximab dose modifications should follow the recommendations in the Rituxan/MabThera package insert and institutional standard practices.

Per the lenalidomide label, the dose adjustments listed in Table 3 are acceptable for lenalidomide.

Table 3 Dose Modification Actions for Lenalidomide

Toxicity	Dose Adjustment
Platelets <50 × 10^9/L:	Interrupt and follow CBC weekly
Platelets return to ≥50 × 10^9/L:	Resume at 5 mg less than previous dose. Discontinue if dose is reduced to <10 mg.
ANC <1.0 × 10^9/L × 7 days or ANC <1.0 × 10^9/L with an associated temperature ≥38.5°C or ANC <0.5 × 10^9/L:	Interrupt and follow CBC weekly
ANC returns to ≥1.0 × 10^9/L:	Resume at 5 mg less than previous dose. Discontinue if dose is reduced to <10 mg.
Other Grade 3/4 toxicities related to lenalidomide:	Hold treatment and restart at the investigator's discretion at the next lower dose when toxicity has resolved to ≤Grade 2

ANC=absolute neutrophil count; CBC=complete blood count.

3.6 CONCOMITANT THERAPY

3.6.1 Permitted Concomitant Therapy

Antiemetics are permitted if clinically indicated. Standard supportive care medications are permitted as per institutional standards.

For subjects considered at risk for TLS: Administer appropriate hydration, and alkalinization of urine, and allopurinol or other prophylaxis for TLS (e.g., rasburicase) per institutional standards before initiating treatment. See further precautions about TLS in Section 3.7.2.

3.6.2 Prohibited Concomitant Therapy

Any chemotherapy, anticancer immunotherapy, corticosteroids (at dosages equivalent to prednisone >20 mg/day for longer than 2 weeks), experimental therapy, or radiotherapy for treating NHL are prohibited. Localized, short courses of radiotherapy are allowed for the treatment of lesions unrelated to the disease under study, if approved by the medical monitor. Subjects may use topical or inhaled corticosteroids or low-dose steroids (≤20 mg of prednisone or equivalent) as therapy for comorbid conditions. During study participation, subjects may also receive systemic or enteric corticosteroids as needed for treatment-emergent comorbid conditions.

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

Do not administer live virus vaccines prior to or during rituximab treatment (Rituxan/MabThera package insert).

3.6.3 Cautionary Therapy Considerations Including Drug-Drug Interactions

Acalabrutinib

The concomitant use of strong inhibitors/inducers of CYP3A (see Appendix 3) should be avoided when possible. Acalabrutinib is a substrate of CYP3A4. Drugs inhibiting CYP3A may increase exposure of acalabrutinib. If a subject requires short-term treatment with a strong CYP3A inhibitor (such as anti-infectives for up to 7 days), interrupt acalabrutinib treatment. If a subject requires a moderate CYP3A inhibitor while on study, monitor the subject closely for potential toxicities.

Conversely, concomitant administration of a strong inducer of CYP3A has the potential to decrease exposure of acalabrutinib and could reduce efficacy. Avoid coadministration of strong CYP3A inducers. 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.

Use of proton-pump inhibitors, H2 receptor antagonists, or antacids while taking acalabrutinib capsules 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 capsules) or antacid (2 hours before or 2 hours after acalabrutinib capsules). Avoid coadministration with proton-pump inhibitors with acalabrutinib capsules. Acalabrutinib maleate tablets can be taken without regards to acid-reducing agents (such as antacids, H2-receptor antagonists, or proton-pump inhibitors).

Lenalidomide

Subjects who are concurrently receiving digoxin should have periodic monitoring of digoxin plasma levels due to increased C_{max} and AUC_{inf} of digoxin with concomitant lenalidomide therapy. Moreover, subjects taking concomitant therapies such as erythropoietin-stimulating agents or estrogen-containing therapies, along with lenalidomide, may have an increased risk of venous thromboembolic events per package insert.

Rituximab

The only drug-drug interaction with rituximab listed in the Rituxan/MabThera package insert is renal toxicity when used in combination with cisplatin.

For additional information on potential drug-drug interactions, refer to the individual drug's package insert and Section 3.7.5.

3.7 RISKS ASSOCIATED WITH STUDY DRUGS

3.7.1 Risks Associated with Acalabrutinib Treatment

Refer to Section 3.5.7 for specific dose modification and discontinuation guidelines.

The following summarizes the experience with acalabrutinib in hematological cancer studies. For more detailed information on treatment-emergent AEs and details regarding the clinical safety of acalabrutinib, refer to the current Acalabrutinib Investigator Brochure.

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 acalabrutinib.

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

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

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

Infections

Serious infections (bacterial, viral, and fungal), including fatal events, have occurred in clinical studies with acalabrutinib. The most frequently reported Grade ≥3 infection was pneumonia (preferred term). Across the acalabrutinib clinical development program (including subjects treated with acalabrutinib in combination with other drugs), cases of HBV reactivation, aspergillosis, and PML have occurred. Please refer to Section 4.1.14 for monitoring of HBV and management of subjects with HBV reactivation.

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

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

Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias, including neutropenia, anemia, and thrombocytopenia have occurred in clinical trials with acalabrutinib. Monitor blood counts as specified in the Schedule of Assessments and as medically appropriate. Please refer to Section 3.5.7 for study drug modification guidance.

Subjects with cytopenias should be managed according to institutional guidelines with

maximal supportive care and diagnostic evaluations as clinically indicated. Subjects should be closely monitored as appropriate.

Second Primary Malignancies

Events of second primary malignancies, including non-melanoma skin carcinomas, have been reported in clinical study 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 medical monitor. Please refer to Section 6.3.3 for second primary malignancy reporting guidance.

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 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. The overall frequency of hepatotoxicity events in acalabrutinib monotherapy pool is low, with the most frequently reported events being ALT elevations and AST elevations. Following a comprehensive review of hepatotoxicity events in the acalabrutinib clinical program, there was insufficient evidence to establish an association between hepatotoxicity events and acalabrutinib due to the contribution of confounding factors, absence of clinical symptoms, and quick recovery without treatment for patients with transaminase elevations. There is limited evidence

regarding hepatotoxicity of non-infectious etiology from literature for other BTK inhibitors.

3.7.2 Risks Associated with Rituximab (Rituxan/MabThera) Treatment

For complete information, refer to the local label for the Reference Safety Information for rituximab for this study and dose modification and discontinuation guidelines (Rituxan/MabThera package insert).

Contraindications

- Hypersensitivity to the active substance or to murine proteins.
- Patients in a severely immunocompromised state.

Warnings and Precautions

The following are a list of warnings and precautions associated with rituximab:

- Fatal infusion reactions within 24 hours of rituximab infusion; approximately 80% of fatal reactions occurred with first infusion. Infusion reactions may be related to release of cytokines and/or other chemical mediators. Cytokine release syndrome may be clinically indistinguishable from acute hypersensitivity reactions
- Severe, including fatal, mucocutaneous reactions such as Toxic Epidermal Necrolysis and Stevens-Johnson syndrome, can occur in subjects receiving rituximab.
- HBV reactivation can occur in patients treated with rituximab, in some cases resulting in fulminant hepatitis, hepatic failure, and death.
- PML, including fatal PML, can occur in subjects receiving rituximab.
- TLS: Administer aggressive intravenous hydration, antihyperuricemic agents, monitor renal function.
- Infections: Withhold rituximab and institute appropriate anti-infective therapy.
- Cardiac adverse reactions: Discontinue infusions in case of serious or life-threatening events.
- Renal toxicity: Discontinue in subjects with rising serum creatinine or oliguria.
- Bowel obstruction and perforation: Consider and evaluate for abdominal pain, vomiting, or related symptoms.

- Live virus vaccines: Live virus vaccinations prior to or during rituximab treatment is not recommended.
- Embryo-fetal toxicity: Can cause neonatal harm. Advise of potential risk to neonates and use of effective contraception.

3.7.3 Risks Associated with Lenalidomide (Revlimid) Treatment

Cases of PML, including fatal cases, have been reported in subjects treated with lenalidomide in combination with immunosuppressive therapy including dexamethasone. Signs and symptoms of PML may include cognitive and behavioral changes, language disturbances, visual disturbances, sensory deficits, weakness, and coordination and gait difficulties. If PML is suspected, hold further treatment with lenalidomide until PML is excluded. If PML is confirmed, lenalidomide will be permanently discontinued.

For complete information refer to the local label Reference Safety Information for lenalidomide (Revlimid package insert) for this study. Also refer to Section 3.5.7 in this protocol for specific dose modification and discontinuation guidelines.

Contraindications

Pregnancy

Lenalidomide can cause fetal harm when administered to a pregnant female. Lenalidomide is contraindicated in females who are pregnant per the package insert.

Allergic Reactions

Lenalidomide is contraindicated in patients who have demonstrated hypersensitivity (e.g., angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to lenalidomide.

Revlimid capsules contain lactose. The risk-benefit of Revlimid treatment should be evaluated in subjects with lactose intolerance per package insert.

Warnings and Precautions

Embryo-fetal Toxicity

If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death (boxed warning). Pregnancy must be excluded before start of treatment.

Hematologic Toxicity

Lenalidomide can cause significant neutropenia and thrombocytopenia (boxed warning).

Venous and Arterial Thromboembolism

Venous thromboembolic events (deep vein thrombosis and pulmonary embolism) and arterial thromboembolic events (myocardial infarction and stroke) are increased in patients treated with lenalidomide and seen in patients treated for multiple myeloma (boxed warning).

Myocardial Infarction

Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors and within the first 12 months when used in combination with dexamethasone. Patients with known risk factors – including prior thrombosis – should be closely monitored, and action should be taken to try to minimize all modifiable risk factors (eg. smoking, hypertension, and hyperlipidemia).

Increased Mortality

Serious and fatal cardiac adverse reactions occurred in patients with CLL treated with lenalidomide.

Second Primary Malignancies

Higher incidences of second primary malignancies were observed in controlled trials of patients with multiple myeloma receiving lenalidomide.

Hepatotoxicity

Hepatic failure, including fatal cases, has occurred in patients treated with lenalidomide in combination with dexamethasone. Monitor liver enzymes as indicated in Section 4.1.12 and stop lenalidomide upon elevation of liver enzymes per the package insert.

Allergic Reactions

Angioedema and serious dermatologic reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported. These events can be fatal. Discontinue lenalidomide if allergic reactions are suspected. Do not resume lenalidomide if these reactions are verified.

Tumor Lysis Syndrome

Fatal instances of TLS have been reported during treatment with lenalidomide. Monitor subjects at risk of TLS (i.e., those with high tumor burden) and take appropriate precautions per the package insert.

Tumor Flare Reaction

Tumor flare reaction has occurred during investigational use of lenalidomide for CLL and lymphoma and is characterized by tender lymph node swelling, low grade fever, pain, and rash. Tumor flare reaction may mimic progression of disease. Lenalidomide may be continued in patients with Grade 1 and Grade 2 tumor flare reaction without interruption or modification per the package insert.

Viral Reactivation Including Hepatitis B Reactivation

Serious or life-threatening reactivation of viral hepatitis may occur in subjects treated with lenalidomide ("Dear Health Care Provider letter November 2016").

Impaired Stem Cell Mobilization

A decrease in the number of $CD34^+$ cells collected after treatment (>4 cycles) with lenalidomide has been reported.

Thyroid Disorders

Both hypothyroidism and hyperthyroidism have been reported.

Pulmonary hypertension

Cases of pulmonary hypertension, some fatal, have been reported in patients treated with lenalidomide. Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease prior to initiating and during lenalidomide therapy.

3.7.4 Dietary Restrictions

All subjects should be strongly cautioned against excessive consumption of grapefruit, grapefruit juice, Seville orange juice or starfruit (which contain potent CYP3A inhibitors) or using herbal remedies or dietary supplements unless approved by the study physician. In particular, St John's wort is a potent CYP3A inducer and should be avoided in subjects treated with acalabrutinib, which is metabolized by CYP3A.

Acalabrutinib taken with an acidic beverage may impact exposure to acalabrutinib (refer to current Acalabrutinib Investigator Brochure and package insert). Acalabrutinib can be taken with or without food.

Otherwise, subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

3.7.5 Drug-Drug Interactions

Drug-drug interactions for individual study drugs are discussed in Section 3.5.3.

Acalabrutinib is predominantly metabolized by CYP3A enzymes and hence can be a

victim of drug-drug interactions. Acalabrutinib is not a clinically relevant inhibitor or inducer of CYP3A enzymes; therefore, drug-drug interactions as a perpetrator is not expected through this pathway.

In vitro data indicates that acalabrutinib is a P-gp and breast cancer resistance protein (BCRP) substrate. However, acalabrutinib is highly permeable and is rapidly and nearly completely absorbed. Thus, an effect of P-gp/BCRP inhibitor on acalabrutinib absorption through P-gp inhibition is not expected. In addition, acalabrutinib has been administered at doses of 200 mg BID and 400 mg QD with acceptable safety and tolerability.

Acalabrutinib may increase exposure to BCRP substrates (e.g., methotrexate) by inhibition of intestinal BCRP and should be coadministered with caution with narrow therapeutic index BCRP substrates.

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

Although the effect of H2-receptor antagonists (such as famotidine or ranitidine) on acalabrutinib absorption has not been evaluated, if treatment with an H2-receptor antagonist is required, the H2-receptor antagonist should be taken approximately 2 hours after acalabrutinib capsules. Acalabrutinib maleate tablets can be taken without regards to acid-reducing agents (such as antacids, H2-receptor antagonists, or proton-pump inhibitors).

For more information on potential drug interactions with acalabrutinib, refer to the current Acalabrutinib package insert and Investigator Brochure.

Rituximab is a monoclonal antibody given intravenously. It is metabolized by catabolism. An effect of rituximab on the pharmacokinetics of the small molecule coadministered drugs and vice versa is not anticipated.

3.7.6 Reproductive Toxicity

Definition of women of non-reproductive potential:

Women will be considered of non-reproductive potential if they are either:

(1) Postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women <45 years of age a high follicle-stimulating hormone [FSH] level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

(2) Have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

(3) Have a congenital or acquired condition that prevents childbearing.

Women of Childbearing Potential (WOCBP)

WOCBP are fertile following menarche and until becoming postmenopausal unless permanently sterile; permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. Postmenopausal state is defined as no menses for at least 12 months without alternative medical cause (FSH in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy; however, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient).

Definition of 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.

Highly effective methods of contraception are‡:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, which may be oral, intravaginal, or transdermal. Note: Estrogens may further increase the risk of thrombosis in patients treated with lenalidomide (see Section 3.7.3).
- Progestogen-only hormonal contraception associated with inhibition of ovulation,

which may be oral, injectable, or implantable

- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomy of a female subject's male partner (with medical assessment and confirmation of vasectomy surgical success)
- Sexual abstinence (only if refraining from heterosexual intercourse during the entire period of risk associated with the study treatments)

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

†Abstinence (relative to heterosexual activity) can only be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs). Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, and postovulation methods) and withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

Results of definitive reproductive toxicity studies with acalabrutinib are provided in the current Acalabrutinib Investigator Brochure.

Women of childbearing potential (see definition of WOCBP potential above) who are sexually active must agree to use highly effective forms of contraception during the study and 2 days after the last dose of acalabrutinib, 12 months after the last dose of rituximab, or 4 weeks after the last dose of lenalidomide, whichever is longer.

Male subjects who are sexually active with a WOCBP partner or a pregnant partner must use a condom during treatment and until 4 weeks after the last dose of lenalidomide or 3 months after the last dose of rituximab. Men must also refrain from donating sperm during the study for 3 months after the last dose of rituximab, or 4 weeks after the last dose of lenalidomide, whichever is longer.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. To participate in the study subjects of childbearing potential must adhere to the contraception

requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 2 days after the last dose of acalabrutinib (for WOCBP only), 12 months after the last dose of rituximab, or 4 weeks after the last dose of lenalidomide, whichever is longer. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

Subjects should promptly notify the investigator if they, or their partners, become pregnant during this period. If a female subject becomes pregnant during the treatment period, she must discontinue study drug immediately. Pregnancy in a female subject or a male subject's partner must be reported as outlined in Section 6.3.4.

Blood Donation

Subjects must not donate blood during treatment with lenalidomide and for 4 weeks after discontinuation of lenalidomide because the bloods might be given to a pregnant female patient whose fetus must not be exposed to lenalidomide.

3.7.7 Overdose Instructions

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an AE unless it results in untoward medical effects.

For any subject experiencing a study drug overdose, observation for any symptomatic side effects should be instituted, and vital signs and biochemical and hematologic parameters should be followed closely. Appropriate supportive management to mitigate adverse effects should be initiated. If the overdose ingestion is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered.

The Sponsor's medical monitor should be contacted if a study drug overdose occurs.

Reporting of Overdose

If an overdose on an investigational medicinal product (IMP) or AstraZeneca non investigational medicinal product (NIMP) occurs in the course of the study, the investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but no later than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety Data Entry Site

(DES). This information should be provided within one (initial fatal/life-threatening or follow-up fatal/life-threatening) or five (other serious initial and follow-up) calendar days for overdoses associated with an SAE (see Section 6.2.2) and within 30 days for all other overdoses.

3.8 WITHDRAWAL OF SUBJECTS FROM STUDY TREATMENT

Subjects may be withdrawn from study treatment for the following reasons:

- Progressive disease
- Completed treatment
- Start of alternative anticancer therapy
- Adverse event
- Pregnancy
- Investigator's decision
- Subject's withdrawal of consent from the study
- Decision by sponsor to terminate the study
- Subject lost to follow-up
- Death
- Other

Subjects who have received ≥1 dose of study drug and discontinue study therapy will continue to be followed on study for follow-up of safety (Section 4.3), disease, time-to-next therapy, and long-term follow-up (Section 4.4) unless they withdraw consent for further follow-up. The date the subject is withdrawn from study treatment or from the study and the reason for discontinuation will be recorded and described on the appropriate eCRF.

3.9 REASONS FOR STUDY EXIT

Reasons for study exit include:

- Subject's withdrawal of consent from study
- Decision by sponsor to terminate the study
- Subject lost to follow-up
- Death

3.10 DATA AND SAFETY MONITORING

This trial will be monitored in accordance with the sponsor's pharmacovigilance procedures. AEs and SAEs will be reviewed internally on an ongoing basis to identify safety concerns. Periodic conference calls with the investigators and applicable site staff will be conducted to discuss study progress, obtain investigator feedback and exchange, and discuss "significant safety events" (i.e., AEs leading to dose modifications, related SAEs, and deaths).

4 STUDY ACTIVITIES AND ASSESSMENTS

The schedule of assessments is provided in Appendix 4 (Part 1), Appendix 5 (Part 2), and Appendix 6 (Part 3). Descriptions of the scheduled evaluations are outlined below and complete information on study drug and dosing is provided in Section 3.5.

Before study entry, throughout the study, and at the follow-up evaluation, various clinical and diagnostic laboratory evaluations are required. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. This study will primarily use central laboratory testing for laboratory evaluations. Samples from local laboratories will be used if central testing is unavailable. All data from local laboratories must be entered in the unscheduled assessment eCRFs.

4.1 DESCRIPTION OF PROCEDURES

4.1.1 Informed Consent

The subject must read, understand, and sign the ICF approved by the IRB/IEC, confirming his or her willingness to participate in this study before initiating any screening activity that is not standard of care. Subjects must also grant permission to use protected health information if required by local regulations.

4.1.2 Medical History

Collect and record the subject's complete history through review of medical records and by interview. Concurrent medical signs and symptoms must be documented to establish baseline severities. A disease history, including the date of initial diagnosis and list of all prior anticancer treatments, and responses and DORs to these treatments, also will be recorded.

4.1.3 Adverse Events

The accepted regulatory definition for an AE is provided in Section 6.2. The AE reporting period is described in Section 6.3.1. All medical occurrences from the time of first dose that meet this definition must be recorded. Important additional requirements for reporting SAEs are explained in Section 6.3.

4.1.4 Concomitant Medications and Therapy

Document all concomitant medications and procedures from within 21 days (Part 1) and 28 days (Parts 2 and 3) before the start of study drug administration through 30 days after the last dose of study drug.

4.1.5 Confirmation of Eligibility

Subject eligibility for enrollment will be assessed per Section 3.4. All screening procedures, unless otherwise indicated, should be completed within 21 days (Part 1) and 28 days (Parts 2 and 3) of the first dose of study drug.

4.1.6 ECOG Performance Status

The ECOG performance index is provided in Appendix 1.

4.1.7 Physical Examination, Vital Signs, Height, and Weight

The physical examination includes height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal, nervous, lymphatic system, and general appearance. The nervous system examination will include attention to neurologic signs and symptoms of PML. The lymphatic system examination will include examination of palpable lymph nodes and spleen and liver below the costal margin on the respective side. Only physicians, physician assistants, or oncology nurse practitioners should perform the lymphatic system examination. As much as possible, the same person should perform all the lymphatic exams for a given subject.

Vital sign measurements (blood pressure, heart rate, respiratory rate, and body temperature) will be assessed after the subject has rested in the sitting position.

4.1.8 Bone Marrow Aspirate and Biopsy

Bone marrow aspirate and biopsy will be performed at screening or up to 60 days before the first dose of study drug (Part 1) or up to 90 days before the first dose of study drug (Parts 2 and 3). Per the current response criteria (Cheson et al. 2014), a bone marrow

aspirate/biopsy will also be required at any time on study to confirm CR (if bone marrow was involved by lymphoma at baseline). Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572. De-identified copies of all bone marrow biopsy/aspirate results may be requested by the sponsor.

Bone marrow will also be used for MRD testing. See Section 4.1.22. When available, any unused bone marrow tissue will be used for PD testing or molecular profiling. PD testing will be performed by the sponsor.

Part 2 and Part 3

An optional bone marrow aspirate and/or biopsy will be performed at the end of treatment for molecular profiling to discover mechanisms of resistance to study treatment.

4.1.9 Electrocardiogram

Subjects should be in supine position and resting for ≥10 minutes before study-related ECGs. At screening, results from the site's ECG machine (12-lead; triplicates taken ≥1 minute apart) will be averaged to determine eligibility and must meet the eligibility criteria of QTcF ≤480 msec. A single ECG will be performed at the end of treatment and safety follow-up visits.

4.1.10 Urine or Serum Pregnancy Test

Pregnancy tests will be required only for women of childbearing potential (a definition for women of nonchildbearing potential is provided in Section 3.7.6). Testing will be performed locally by use of central laboratory provided kits. Pregnancy testing may be performed by local laboratories and can be done more frequently than the protocol-defined schedule, if required by local regulatory authorities.

4.1.11 Hematology

Hematology laboratory testing must include complete blood count with differential and platelet counts. Testing will be performed by the central laboratory at screening and at each clinic visit.

4.1.12 Serum Chemistry

Chemistry must include albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen, bone-specific alkaline phosphatase, calcium, chloride, creatinine, glucose, LDH, magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin, total

protein, and uric acid. If results from an unscheduled ECG are abnormal and considered clinically significant at any time, then an electrolyte panel (i.e., calcium, magnesium, and potassium) must be obtained to coincide with the ECG testing. Testing will be performed by the central laboratory at screening and at each clinic visit.

4.1.13 Thyroid Function Test

Part 3

Subjects receiving lenalidomide should be monitored for hyperthyroidism and hypothyroidism. Thyroid laboratory testing must include thyroid-stimulating hormone, triiodothyroxine, and thyroxine. Testing will be performed by the central laboratory at screening and every 12 weeks during treatment with lenalidomide and 12 weeks after the last dose of lenalidomide.

4.1.14 Hepatitis B and C Testing

Hepatitis serology testing at screening must include HBsAg, hepatitis B surface antibody (anti-HBs), anti-HBc, and HCV antibody. In addition, any subject testing positive for anti-HBc or HCV antibody, must have additional PCR testing performed during screening (see Appendix 4, Appendix 5, and Appendix 6). Testing will be performed by a local or central laboratory.

Since IVIG may cause false positive hepatitis serology, subjects who are receiving prophylactic IVIG and have positive HBsAg or anti-HBc must have negative hepatitis B DNA to be eligible. Those who are HBsAg positive or hepatitis B PCR positive and those who are hepatitis C PCR positive will be excluded.

Subjects who are anti-HBc positive should have HBV DNA PCR performed during screening and monthly 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.

Subjects with a known history of hepatitis C or who are hepatitis C antibody positive should be tested by quantitative PCR for HCV RNA during screening. Such subjects may be enrolled provided the quantitative PCR is negative (undetectable viral load). No further monitoring for HCV RNA during treatment is necessary if initial PCR results are negative.

Refer to Section 3.7.1 and Appendix 4, Appendix 5, and Appendix 6 regarding monitoring of subjects who are anti-HBc positive or hepatitis C antibody positive or have a known history of HBV.

4.1.15 Urinalysis

Urinalysis includes pH, ketones, specific gravity, bilirubin, protein, blood, and glucose. Testing will be performed by the central laboratory.

4.1.16 T/B/NK Cell Count

Flow cytometry testing will include $CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, and $CD16^+/56^+$ cells. Testing will be performed by the central laboratory.

4.1.17 Serum Immunoglobulin

Testing for immunoglobulin (Ig) G, IgM, and IgA will be performed by the central laboratory.

4.1.18 Endoscopy and ^{13}C Urea Breath Test for Gastric MALT Lymphoma Subjects

Part 2

Subjects with gastric MALT lymphoma will have an endoscopy performed at screening or up to 90 days before the first dose of study drug. Endoscopies will also be required at any time on study to confirm CR. Testing will be performed at the study center.

A ^{13}C urea breath test will be performed at screening only if the subject does not have H. pylori results from a pathology report. If this test is needed, proton-pump inhibitors and H2 blockers must be discontinued or withheld 14 days and 7 days, respectively, and antibiotics for treating H. pylori, such as those with anti-helicobacter action and bismuth preparations, should be withheld at least 30 days before the test.

4.1.19 Pharmacokinetics

Part 1

Refer to the laboratory binder for instructions on collecting and processing these samples. Testing will be performed at a central clinical laboratory. Leftover plasma samples may be used for exploratory acalabrutinib metabolite analyses. PK samples

will be drawn per Table 4.

Table 4 Pharmacokinetic Sample Schedule

Cycle	Day	Predose	Hours Postdose					
			0.5 (±5 min)	0.75 (±5 min)	1 (±5 min)	2 (±10 min)	4 (±10 min)	6 (±10 min)
1	1	x	x	x	x	x	x	x
	8	x	x	x	x	x	x	x
	15, 22	x			x			
2	1	x						

min=minute.

Part 2

PK sampling will not be performed in this part of the study.

Part 3

PK sampling will be performed, and sparse PK samples will be drawn per Schedule of Assessments (Appendix 6). Refer to the laboratory manual for instructions on collecting and processing these samples. Testing will be performed at a central clinical laboratory. The remaining plasma samples may be used for exploratory biomarker development or acalabrutinib metabolite and/or lenalidomide analyses. PK samples will be drawn per Table 5.

Table 5 Sparse PK Sampling Schedule for Part 3

Cycle	Day	Record Time of Dose	After Acalabrutinib Dose	
			1 Hour (±5 minutes)	4 Hours (±10 minutes)
1	1	x	x	x
	8	x	x	x
2	1	x	x	x

4.1.20 Pharmacodynamics

Blood samples and bone marrow, when available, will be used for PD testing (e.g., BTK occupancy and BTK function). Refer to Appendix 4, Appendix 5, and Appendix 6 and the laboratory binder for sampling times and instructions on collecting and processing

these samples. Testing will be performed by the sponsor.

4.1.21 Molecular Profiling

Part 1

No molecular profiling will be performed.

Part 2 and Part 3

[redacted]

4.1.22 Tumor Assessment

A pretreatment CT scan with contrast (unless contraindicated) is required of the chest, abdomen, and pelvis and any other disease sites (e.g., neck) within 30 days before the first dose of study drug. A pretreatment positron-emission tomography (PET)/CT scan within 60 days before the first dose is also required. Information on extranodal involvement will also be recorded.

During treatment, CT scans with contrast (unless contraindicated) of the chest, abdomen, and pelvis and any other disease sites (e.g., neck) will be performed for tumor assessments.

For subjects in Part 1, CT scans will be performed at Day 1 of Cycle 3 (±7 days), Cycle 5 (±7 days), and Cycle 7 (±7 days); and then every 3 cycles (12 weeks, ±7 days) thereafter up to 2 years then every 6 cycles (24 weeks) or more frequently at the investigator's discretion.

For subjects in Part 2 and Part 3, CT scans will be performed for tumor assessments every 3 cycles (12 weeks, ±7 days) starting at Day 1 of Cycle 4, Cycle 7, Cycle 10, and Cycle 13, then every 24 weeks thereafter or more frequently at the investigator's discretion.

On-study tumor assessments will also include physical examination and laboratory test results. Bone marrow (if involved by lymphoma at baseline), endoscopy (for subjects with gastric MALT), and PET/CT are required to confirm CR per clinical guidelines (see Section 3.2). For subjects participating in Part 3, PET/CT scans will be performed at Cycle 4 Day1 (Week 12), and Cycle 7 Day 1 (Week 24), and at CR.

De-identified copies of all radiology results maybe requested by the sponsor.

Subjects should have radiographic tumor measurements performed at the participating study center or an acceptable alternate imaging facility using an identical imaging

protocol and similar equipment. The same imaging equipment should be used for all scans whenever possible. The same radiologist should be assigned to read all the scans for a given subject throughout the study.

Up to 6 measurable nodal and extranodal lesions (i.e., per Lugano Classification, measurable nodes >1.5 cm in longest diameter and measurable extranodal lesions >1.0 cm in longest diameter may be assessed). 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. 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.

In the event disease progression is suspected due to results from physical examinations or laboratory tests, a CT and or PET/CT scan must be performed to confirm disease progression. It is required that disease progression identified by PET/CT alone be confirmed by an alternative imaging modality (e.g., diagnostic quality CT) or by biopsy. There must be radiologically measurable disease at screening (≥1 nodal lesion >2.0 cm in the longest diameter, and/or extranodal session >1.0 cm in the longest diameter). If the sole lesion lies within the field of prior radiotherapy, there must be evidence of disease progression in that lesion.

Subjects with confirmed CR are not required to undergo further PET/CT scans on study. If disease progression on CT is suspected but cannot be biopsy-proven, PET/CT may be used at the investigator's discretion.

A central imaging vendor may be used to collect and store imaging data in the event the sponsor chooses to perform independent radiologic assessments.

Part 2 and Part 3

Minimal Residual Disease Testing

Minimal residual disease (MRD) testing will be performed on tumor biopsy, peripheral blood, and bone marrow samples by a central laboratory. Baseline (pretreatment) tumor tissue (i.e., diagnostic/predose archival lymph node, bone marrow, or tumor tissue) will be collected from each subject at screening. A blood sample is to be collected within 12 weeks for subjects with radiological confirmation of CR or PR and at the end of treatment visit for subjects who discontinue study treatment for any reason. For subjects with

lymphoma involvement of bone marrow at baseline, the bone marrow biopsy performed for CR confirmation should also be collected for MRD evaluation. MRD determination will be an exploratory analysis for correlation with outcome on trial and the MRD testing results will not be used for making any treatment decisions on study. Refer to the laboratory manual for processing and shipping of samples.

4.1.23 Study Drug Accountability

See Section 7.11.

4.1.24 Routine Clinical Assessments

Routine clinical assessments include physical examinations, recording of symptoms, and laboratory evaluations to evaluate for both AEs and assessment of disease progression at times when the CT or PET/CT scan is not obtained. The investigator should report any suspected disease progression to the sponsor or designee.

4.2 INVESTIGATOR'S ASSESSMENT OF RESPONSE TO TREATMENT

The investigator must rate the response of the subject's response to treatment consistent with clinical guidelines (Cheson et al. 2014) as listed below in Table 6.

Overall response assessments will include evaluation of physical examinations, bone marrow assessments, and radiographic evaluations per the schedule of assessments. Subjects who have signs and symptoms of progression outside of the scheduled assessment should be evaluated by the investigator with a physical examination and response assessments (see Table 6) to determine if disease progression is present. Any suspected case of disease progression should be confirmed with a CT and/or PET/CT scan if one was not obtained and should be reported to the Sponsor or designee via the electronic data capture (EDC) system. Subjects may continue study treatment until progression is confirmed.

Table 6 Response Assessment Criteria for NHL (Cheson et al. 2014)

Response and Site	PET-CT-Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extra lymphatic sites	Score 1, 2, or 3[a] with or without a residual mass on 5PS[b] It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.	Target nodes/nodal masses must regress to ≤1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in the marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extra lymphatic sites	Score 4 or 5[b] with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value When no longer visible, 0 × 0 mm For a node >5 mm × 5 mm, but smaller than the normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
New lesions	None	None

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

Response and Site	PET-CT-Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

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

a A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to 6 of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in 2 diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, and lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

b PET 5PS: 1, no uptake above background; 2. Uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

4.3 SAFETY FOLLOW-UP VISIT

Each subject should be followed for 30 (+7) days after his or her last dose of study drug (i.e., the "safety follow-up visit") until the final data cut-off to monitor for resolution or progression of AEs (see Section 6.3.6) and to document the occurrence of any new events regardless of whether the subject receives a new anticancer therapy or demonstrates disease progression within this timeframe. Subjects who withdraw consent should still be encouraged to complete the safety follow-up assessments, but these assessments cannot be mandated once consent is withdrawn. The Schedule of Assessments (Appendix 4, Appendix 5, and Appendix 6) describes the procedures

required for the safety follow-up.

4.4 TIME-TO-NEXT TREATMENT, DISEASE FOLLOW-UP, AND LONG-TERM FOLLOW-UP

Part 1

Subjects who discontinue study therapy and complete the 30-day safety follow-up will continue on study for follow-up of time-to-next treatment unless they withdraw consent for further follow-up (Appendix 4). Thus, all subjects receiving ≥1 dose of study drug will be followed during the immediate post-therapy period with long-term follow-up (LTFU) assessments unless the subject withdraws consent for such follow-up to be conducted. The date the subject is withdrawn from the study and the reason for discontinuation will be recorded and described on the appropriate eCRF.

Part 2 and Part 3

Subjects who have received ≥1 dose of study drug, discontinue study therapy, and complete the 30-day safety follow-up, will continue on study for follow-up of disease (for subjects who discontinued for reasons other than disease progression), time-to-next treatment, and survival unless they withdraw consent for further follow-up. All follow-up visits should occur approximately every 12 weeks (see Appendix 5 and Appendix 6 for detailed information):

1. Disease follow-up: Subjects who discontinue for reasons other than disease progression will be followed for disease progression (via CT scans per investigator discretion), regardless of whether the subjects receive a new anticancer therapy. The time-to-next treatment information will also be collected. Subjects will then continue long-term follow-up (see #2 below).
2. Long-term follow-up: Subjects who have disease progression, regardless of whether disease progression occurred during the study treatment period or the disease follow-up period, will be followed for time-to-next treatment and survival until death, lost to follow-up, or consent withdrawal.

The date the subject is withdrawn from the study and the reason for discontinuation will be recorded and described on the appropriate eCRF.

4.5 MISSED EVALUATIONS

Missed evaluations should be rescheduled and performed as close to the original scheduled date as possible. An exception is made when rescheduling becomes, in the

investigator's opinion, medically unnecessary or unsafe because it is too close in time to the next scheduled evaluation. In that case, the missed evaluation should be abandoned.

5 STATISTICAL METHODS OF ANALYSIS

5.1 GENERAL CONSIDERATIONS

Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions for discrete variables) will be used to summarize data as appropriate. All analyses will be done by indication, treatment, and overall.

5.2 SAMPLE SIZE CONSIDERATIONS

Part 1

This study will assess acalabrutinib safety, PK, PD, and antitumor activity when administered alone or in combination with rituximab. A total of 24 subjects (12 each arm) in the Relapsed/Refractory Cohort will be equally randomized into 1 of 2 treatment arms (monotherapy and combination therapy). Twelve subjects will be enrolled to the Treatment-naive Cohort receiving the combination therapy. The study is not formally designed to compare these regimens but rather to obtain descriptive information that can be used in support of further acalabrutinib development.

The primary objective of this study is to determine the safety as such:

- With a total sample size of 36, the probability of observing one or more instances of an AE with a background rate of 5% and 10% is 84% and 98%, respectively.
- For each treatment arm (n=12 each), the probability of observing one or more instances of an AE with a background rate of 5% and 10% is 46% and 72%, respectively.
- This provides reasonable assurance for generating preliminary safety data for this Phase 1b, proof-of-concept study.

Part 2

Part 2 will enroll up to 40 subjects in Cohort 1. The primary objective is to characterize the activity of acalabrutinib alone in subjects with R/R MZL as measured by the ORR. Up to 40 subjects in treatment Cohort 1 will provide data for an initial assessment of safety and efficacy of acalabrutinib treatment. Sample size is not based on statistical power consideration.

Part 3

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

5.3 DEFINITION OF ANALYSIS SETS

The following definitions will be used for the efficacy and safety analysis sets.

All-treated population: All randomized or enrolled subjects who receive ≥1 dose of study drug.

Efficacy-evaluable population: All subjects in the All-treated population who have ≥1 response assessment after the first dose of study treatment.

The safety analyses and primary efficacy analyses for all efficacy endpoints will be performed on the All-treated population. Sensitivity analyses for efficacy will be carried out on the Efficacy-evaluable population.

5.4 MISSING DATA HANDLING

General Considerations: Subjects lost to follow-up (or who dropped out) will be included in statistical analyses up to the point of their last evaluation.

Duration of Response and Progression-Free Survival: Data for subjects without disease progression or death will be censored at the date of the last tumor assessment and before the initiation of alternative anticancer therapy. The details of the censoring rules will be provided in the Statistical Analysis Plan (SAP).

Time-to-Next Treatment: Data from subjects who have not received subsequent therapy will be censored at the earliest of death or the last time that lack of administration of a new therapy was objectively documented. The details of the censoring rules will be provided in the SAP.

Safety: Missing or partial start and end dates for AEs and concomitant medications will be imputed according to prespecified, conservative imputation rules. The details will be provided in the SAP. No other imputation of values for missing data will be performed.

5.5 ENDPOINT DATA ANALYSIS

5.5.1 Safety Endpoint

Safety summaries will include summaries in the form of tables and listings. The

frequency (number and percentage) of treatment emergent AEs will be reported in each treatment group by MedDRA System Organ Class and Preferred Term. Summaries will also be presented by the severity of the AE (per CTCAE, v4.03 for Part 1 and v5.0 for Parts 2 and 3) and by relationship to study drug.

Laboratory shift tables containing counts and percentages will be prepared by treatment assignment, laboratory parameter, and time. Summary tables will be prepared for each laboratory parameter. Figures of changes in laboratory parameters over time will be generated.

Results of vital sign assessments and physical exams will be tabulated and summarized.

5.5.2 Demographics and Baseline Characteristics

Additional analyses will include summaries of subject demographics, baseline characteristics, medical history, compliance, and prior and concurrent treatments. Concomitant medications will be coded according to the World Health Organization (WHO) Drug Dictionary and tabulated.

5.5.3 Study Treatment Administration and Compliance

Descriptive information will be provided regarding the number of acalabrutinib, lenalidomide, and rituximab doses prescribed, the total number of doses taken, the number of days of treatment, and the number and timing of prescribed dose reductions and interruptions.

For each subject, acalabrutinib and lenalidomide compliance will be described in terms of the proportion of study drug actually taken based on returned pill count relative to the amount that was dispensed (taking into account physician-prescribed modifications and interruptions).

5.5.4 Analysis of Efficacy Parameters

Overall Response Rate

ORR will be defined as the proportion of subjects who achieve a CR or PR according to the Lugano Classification for NHL (Cheson et al. 2014), as assessed by investigators. ORR will be calculated, and the corresponding 2-sided confidence interval will be derived.

Duration of Response

The DOR is defined as the interval from the first documentation of CR or PR to the earlier of the first documentation of definitive disease progression or death from any cause. Kaplan-Meier methods will be used to estimate event-free curves and

corresponding quantiles (including the median).

Progression-Free Survival

PFS is defined as the interval from the start of acalabrutinib therapy to the earlier of the first documentation of objective disease progression or death from any cause. Kaplan-Meier methods will be used to estimate the event-free curves and corresponding quantiles (including the median).

Time-to-Next Treatment

Time-to-next treatment defined as the time from start of acalabrutinib therapy on this protocol to the start of the next treatment. Kaplan-Meier methods will be used to estimate the event-free curves and corresponding quantiles (including the median). Data from subjects who have not received subsequent therapy will be censored at the earliest of death or the last time that lack of administration of a new therapy was objectively documented.

Time-to-next treatment data will be collected from subjects in Part 2 and Part 3 for an exploratory analysis.

Overall Survival

The duration of OS will be measured from the start of acalabrutinib therapy until the date of death. Subjects who are known to be alive as of their last known status will be censored at their date of last contact. Kaplan-Meier methodology will be used to estimate OS curves and corresponding quartiles (including the median).

5.5.5 Analysis of Pharmacokinetic/Pharmacodynamic Parameters

Part 1

The plasma pharmacokinetics of acalabrutinib in subjects receiving acalabrutinib alone or in combination with rituximab will be characterized using noncompartmental analysis. The following PK parameters will be calculated, whenever possible, from plasma concentrations of acalabrutinib:

- AUC_{0-t} Area under the plasma concentration-time curve calculated using linear trapezoidal summation from time 0 to time t, where t is the time of the last measurable concentration (C_t).
- AUC_{0-12} Area under the plasma concentration-time curve from 0 to 12 hours, calculated using linear trapezoidal summation.
- $AUC_{0-\infty}$ Area under the plasma concentration-time curve from 0 to infinity,

calculated using the formula: $AUC_{0-\infty} = AUC_{0-t} + C_t / \lambda_z$, where λ_z is the apparent terminal elimination rate constant.

- $AUC_{0-24calc}$ Area under the plasma concentration-time curve from 0 to 24 hours, calculated by doubling the value for AUC_{0-12}.
- C_{max} Maximum observed plasma concentration
- T_{max} Time of the maximum plasma concentration (obtained without interpolation)
- $t_{½}$ Terminal elimination half-life (whenever possible)
- λ_z Terminal elimination rate constant (whenever possible)
- CL/F Oral clearance
- Vz/F Oral volume of distribution

The PK parameters will be tabulated and summarized using descriptive statistics.

Part 2: There will be no PK analysis in Part 2.

Part 3

Plasma concentrations of acalabrutinib and ACP-5862 will be tabulated for each subject by arm, visit, and timepoint. Summary statistics (mean, median, standard deviation, percentage coefficient of variation) and plots will be presented, as appropriate.

Additional analyses, including population PK analysis, may be conducted as appropriate.

Part 1, Part 2, and Part 3

Missing dates or times may be imputed for PK and PD samples if the missing values can be established with an acceptable level of accuracy based on other information obtained during the visit in question. If PK and PD sampling for a given subject is not performed according to protocol instructions, that subject may be excluded from the PK and PD analyses.

For each PD variable, the concentration at each assessment will be described. The change from baseline to each assessment will be summarized. The best change from baseline during the study will also be summarized. As appropriate, the on-treatment values will be compared with the pretreatment baseline values using paired t-tests. P-values of ≤ 0.05 will be considered significant.

5.5.6 Explorative or Correlative Analyses

Additional PK or PD analyses may be performed, as deemed appropriate.

Correlations between subject characteristics and outcome measures and correlations among outcomes measures will be explored using regression models or other appropriate techniques.

6 ASSESSMENT OF SAFETY

Safety assessments will consist of monitoring and recording AEs and SAEs; measurements of protocol-specified hematology, clinical chemistry, urinalysis, and other laboratory variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s).

6.1 REFERENCE SAFETY INFORMATION

For the purpose of reporting AEs and SAEs:

- The Investigator Brochure contains the Reference Safety Information (RSI) for acalabrutinib

6.2 DEFINITIONS

6.2.1 Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational (medicinal) product, regardless of attribution of causality.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with NHL that were not present before the AE reporting period (see Section 6.3.1).
- Pre-existing medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Abnormal laboratory values considered clinically significant by the investigator should be reported as an AE. For actions required for liver toxicity, refer to Appendix 7.

The following are NOT considered an AE:

- Pre-existing condition that has not worsened: A pre-existing condition (documented on the medical history eCRF) is not considered an AE unless the

severity, frequency, or character of the event worsens during the reporting period.

- Preplanned hospitalization: A hospitalization planned before signing the ICF is not considered an SAE but rather a therapeutic intervention. However, if during the preplanned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before signing the ICF, will not be considered serious if they are performed after signing the ICF for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances are also not considered SAEs.
- Diagnostic testing and procedures: Testing and procedures should not be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported. If a test or procedure is performed to rule out a diagnosis, the sign or symptom leading to the test/procedure should be the event term, and the event term should only be updated to the diagnosis if/when a diagnosis is confirmed. Testing and procedures performed solely as screening measures (e.g., routine screening mammography or colonoscopy) should not be reported as AEs or SAEs.
- Abnormal laboratory results the investigator considers to not be clinically significant: Abnormal laboratory results are not AEs unless they are clinically significant. For example, a clinically significant laboratory result is one that requires treatment (for example a blood transfusion for low hemoglobin) or requires a change in study drug (e.g., lowering the dose or withholding study drug while the laboratory finding resolves or stabilizes).
- Progression of underlying malignancy: Progression of underlying malignancy will not be reported as an AE if it is clearly consistent with the suspected progression of the underlying cancer. 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.
- 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.

6.2.2 Serious Adverse Event

The terms “severe” and “serious” are not synonymous. Severity (or intensity) refers to the grade of an AE (see below). “Serious” is a regulatory definition and is based on subject or event outcome or action criteria usually associated with events that pose a threat to a subject’s life or functioning. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities.

An AE should be classified as an SAE if it meets any 1 of the following criteria:

- It results in death (i.e., the AE actually causes or leads to death)
- It is life-threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death at the time of the event. It does not include an AE that, had it occurred in a more severe form, might have hypothetically caused death)
- It requires or prolongs inpatient hospitalization
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject’s ability to conduct normal life functions)
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above)

6.2.3 Adverse Events of Special Interest

The following events are adverse events of special interest (AESIs) for subjects randomized to the acalabrutinib-containing combinations arm and must be reported to the Sponsor expeditiously (see Section 6.3.5 for reporting instructions), irrespective of regulatory seriousness criteria or causality.

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

For study treatment containing biologic products:

- Suspected transmission of an infectious agent by the study drug whereby any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic is

considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings indicating an infection in a subject exposed to a medicinal product. This term ONLY applies when a contamination of the study drug is suspected, NOT for infections supported by the mode of action, e.g., immunosuppression.

6.2.4 Severity

Definitions found in the CTCAE (Version 4.03 for Part 1 and Version 5.0 for Parts 2 and 3) will be used for grading the severity (intensity) of AEs. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences that are usually transient, requiring no special treatment, and not interfering with the subject's daily activities
- Grade 2 (Moderate AE) – experiences that introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures
- Grade 3 (Severe AE) – experiences that are unacceptable or intolerable, significantly interrupt the subject's usual daily activities, and require systemic drug therapy or other treatment
- Grade 4 (Life-threatening or disabling AE) – experiences that cause the subject to be in imminent danger of death
- Grade 5 (Death due to AE) – experiences that result in subject death

6.3 DOCUMENTING AND REPORTING OF ADVERSE AND SERIOUS ADVERSE EVENTS

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, as outlined in the prior sections, are recorded on the eCRF. All SAEs also must be reported using the SAE report form (see Section 6.3.5).

All SAEs, overdoses, and pregnancies must continue to be reported after the final data cut-off. Follow-up to existing SAEs must be entered in the clinical database. AEs will no longer be reported in the clinical database after final data cut-off but will instead be recorded in the subject's medical record. After database lock, all new or follow-up to existing SAEs and pregnancies must be reported on the SAE paper form.

6.3.1 Adverse Event Reporting Period

AEs and SAEs will be collected by the site from time of signature of ICF throughout the treatment period and including the follow-up period. After the signing of the ICF and prior to the first dose of study drug, all SAEs, regardless of causality, must be reported to the Sponsor.

All AEs and SAEs will be reported from first dose of study treatment until 30 days after the last dose of study drug(s) 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 drug(s) or any AEs of concern (deemed by the Sponsor or investigator), regardless of causality to the study drug(s) 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 the subject is lost to follow-up or withdraws consent. Resolution/stable means the subject has returned to baseline state of health or the investigator does not expect any further improvement or worsening of the event.

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

Investigators are not obligated to actively seek AE or SAE 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.

After the final DCO, the study will transition to the PTAP. Patients will be managed as per standard of care. All SAEs, irrespective of attribution of causality, will be collected and recorded in the subject's medical records. SAEs will be reported to the sponsor using a paper form via Fax or email. No AEs will be reported during the PTAP phase of the study.

6.3.2 Assessment of Adverse Events

Investigators will assess the occurrence of AEs and SAEs at all subject evaluation timepoints during the study. All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, or other means will be recorded in the subject's medical record and on the AE eCRF.

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

Each recorded AE or SAE will be described by its diagnostic term, duration (i.e., start and end dates), severity, regulatory seriousness criteria, if applicable, suspected relationship to the study drug (see following guidance), and any actions taken in regard to the event. The causal relationship of AEs to the study drug will be assessed by means of the question: "Is there a reasonable possibility that the event may have been caused by the study drug?" per FDA guidance on safety reporting requirements (FDA Safety Reporting Requirements for INDs and BA/BE Studies (December 2012)).

See Appendix 2 for more detail on assessing causality.

6.3.3 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 fulfill 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 (IP) under study and is not the development of new or progression of existing metastasis to the tumor under study). Malignant tumors that—as part of normal, if rare, progression—undergo transformation (e.g., Richter's transformation of B-cell chronic lymphocytic leukemia into DLBCL) should not be considered a new malignant tumor.

6.3.4 Pregnancy

The investigator should report all pregnancies and pregnancies in the partners of subjects within 24 hours using the Pregnancy Report Form. This form should be faxed or emailed to the Sponsor’s Drug Safety. Any pregnancy-associated SAE must be

reported to the Sponsor, using the SAE report form, according to the usual timelines and directions for SAE reporting (Section 6.3.5).

Any uncomplicated pregnancy that occurs with the subject or with the partner of a treated subject during this study will be reported for tracking purposes only, if agreed to by the subject or the partner of the subject in this study. All pregnancies and partner pregnancies that are identified during or after this study, wherein the estimated date of conception is determined to have occurred from the time of consent to 2 days after the last dose of acalabrutinib, 12 months after the last dose of rituximab, or 4 weeks after the last dose of lenalidomide (whichever is longer) will be reported, followed to conclusion, and the outcome reported, as long as the subject or partner is willing to participate in follow-up.

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

Subjects should be instructed to immediately notify the investigator of any pregnancies. Any female subjects receiving study treatment who become pregnant must immediately discontinue study drug. The investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus. Upon completion of the pregnancy, additional information on the mother, pregnancy, and baby will be collected and sent to DrugSafety@acerta-pharma.com.

Drug Safety Contact Information	
Fax:	+1 866 467 0304 (United States) +1 650 935 4996 (for outside the United States)
Email:	DrugSafety@acerta-pharma.com

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

All SAEs and AESIs must be reported within 24 hours of discovery. Initial SAE/AESI reports and follow-up information will be reported using the protocol-specific electronic data capture system according to the investigator site file. If electronic SAE reporting is not available, paper SAE/AESI forms must be completed and emailed or faxed to the

Sponsor's Drug Safety department, or designee. The Sponsor may request follow-up and other additional information from the investigator (e.g., hospital admission/discharge notes and laboratory results). After final database lock, new or follow-up to existing SAEs will be reported using a paper form.

Whenever possible, AEs/SAEs should be reported by diagnosis term not as a constellation of symptoms.

Death due to disease progression should be recorded on the appropriate form in the EDC system. If the primary cause of death is disease progression, then the death due to disease progression should not be reported as an SAE. If the primary cause of death is something other than disease progression, then the death should be reported as an SAE with the primary cause of death as the event AE term, as death is typically the outcome of the event, not the event itself. The primary cause of death on the autopsy report should be the term reported. Autopsy and postmortem reports must be forwarded to the Sponsor's Drug Safety department, or designee, as outlined above.

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

An SAE may qualify for mandatory expedited reporting to regulatory authorities if the SAE is attributable to the investigational product and is not listed in the current Investigator's Brochure (i.e., an unexpected event). In this case, the Sponsor's Drug Safety department or designee will forward a formal notification describing the Suspected Unexpected Serious Adverse Reaction (SUSAR) to all investigators. Each investigator must then notify his or her IRB/IEC of the SUSAR.

Drug Safety Contact Information	
	+1 866 467 0304 (United States)
Fax:	+1 650 935 4996 (for outside the United States)
Email:	DrugSafety@acerta-pharma.com

6.3.6 Type and Duration of Follow-up of Subjects After Adverse Events

All AEs and SAEs that are encountered during the protocol-specified AE reporting period should be followed to resolution, or until the investigator assesses the event as stable, a new anticancer therapy is initiated, or the subject is lost to follow-up or withdraws consent.

6.3.7 Medication Error, Drug Abuse, and Drug Misuse

Timelines

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

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within **one** (initial fatal/life-threatening or follow-up fatal/life-threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the event of medication error, drug abuse, or misuse (see Section 6.2.2) and **within 30 days** for all other events.

Medication Error

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

The full definition and examples of medication error can be found in Appendix 9.

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 9.

Drug Misuse

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

The full definition and examples of drug misuse can be found in Appendix 9.

7 STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

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

- Unsatisfactory subject enrollment with regard to quality or quantity

- Significant or numerous deviations from study protocol requirements, such as failure to perform required evaluations on subjects and maintain adequate study records
- Inaccurate, incomplete or late data recording on a recurrent basis
- The incidence and/or severity of AEs in this or other studies indicating a potential health hazard caused by the study treatment

7.1 REGULATORY AND ETHICAL COMPLIANCE

Ethical Conduct of the Study

This clinical study was designed and will be implemented in accordance with the protocol, the International Conference on Harmonisation Harmonized Tripartite Guidelines for Good Clinical Practices, applicable local regulations (including US Code of Federal Regulations (CFR) Title 21 and European Directive 2001/20/EC), and the ethical principles laid down in the Declaration of Helsinki (October 2008).

Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to AstraZeneca of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study intervention under clinical investigation are met.

AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. AstraZeneca will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

For all studies except those utilizing medical devices, investigator safety reports must be prepared for SUSAR according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

Adherence to European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from AstraZeneca will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches

Prompt notification by the investigator to the sponsor of any (potential) serious breach

of the protocol or regulations is essential so that legal and ethical obligations are met.

- A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.

If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.

In certain regions/countries, the sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.

- The sponsor will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, the sponsor is required to enter details of serious breaches into the European Medicines Agency (EMA) Clinical Trial Information System (CTIS). It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.

The investigator should have a process in place to ensure that:

- the site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach
- a (potential) serious breach is promptly reported to the sponsor or delegated party, through the contacts (e-mail address or telephone number) provided by the sponsor.

7.2 INSTITUTIONAL REVIEW BOARD AND INDEPENDENT ETHICS COMMITTEE

After the final data cut-off, the investigator will continue submitting any amendments to the protocol, the informed consent, Investigator Brochure, and any other relevant information to the appropriate IRB/IEC for review and approval. A signed protocol approval page; a letter confirming IRB/IEC approval of the protocol and informed consent; and a statement that the IRB/IEC is organized and operates according to Good Clinical Practice (GCP) guidelines and the applicable laws and regulations; **must** be forwarded to the Sponsor or representative. Amendments to the protocol must also be approved by the local regulatory agency, as appropriate, before the implementation of changes in this study.

7.3 INFORMED CONSENT AND PROTECTED SUBJECT HEALTH

INFORMATION AUTHORIZATION

A copy of the IRB/IEC-approved ICF must be forwarded to the Sponsor for regulatory purposes. The investigator, or designee (designee must be listed on the Study Personnel Responsibility/Signature Log, see Section 7.11), **must** explain to each subject the purpose and nature of the study, the study procedures, the possible adverse effects, and all other elements of consent as defined in § 21CFR Part 50, and other applicable national and local regulations governing informed consent. Each subject must provide a signed and dated ICF before enrollment into this study. If allowed by the protocol, a legal representative may sign the informed consent form for a subject incapable of giving consent. Signed consent forms must remain in each subject's study file and be available for verification by study monitors at any time.

In accordance with individual local and national patient privacy regulations, the investigator or designee **must** explain to each subject that for the evaluation of study results, the subject's protected health information obtained during the study may be shared with the Sponsor and its designees, regulatory agencies, and IRBs/IECs. As the study Sponsor, the Sponsor will not use the subject's protected health information or disclose it to a third party without applicable subject authorization. It is the investigator's or designee's responsibility to obtain written permission to use protected health information from each subject, or if appropriate, the subject's legal guardian. If a subject or subject's legal guardian withdraws permission to use protected health information, it is the investigator's responsibility to obtain the withdrawal request in writing from the subject or subject's legal guardian **and** to ensure that no further data will be collected from the subject. Any data collected on the subject before withdrawal will be used in the analysis of study results.

7.4 CASE REPORT FORMS

Authorized study site personnel (see Section 7.11) will complete eCRFs designed for this study according to the completion guidelines that will be provided. The investigator will ensure that the eCRFs are accurate, complete, legible, and completed promptly. For record retention policies, refer to Section 7.6.

After the final data cut-off, the clinical database will close to new data collection and will be archived accordingly.

7.5 STUDY MONITORING REQUIREMENTS

Representatives of the Sponsor or its designee will monitor this study until completion.

Monitoring will be conducted through personal visits with the investigator and site staff as well as any appropriate communications by mail, fax, email, or telephone. The purpose of monitoring is to ensure compliance with the protocol and the quality and integrity of the data. This study is also subject to reviews or audits by the sponsor, regulatory authorities, or ethics committees.

Remote Monitoring Visits

The main goal of a Remote Monitoring Visit is to check the status of ongoing patients, check IMP supply needs and provide support.

Onsite Monitoring Visits

The main goal of an Onsite Monitoring Visit is site oversight, verification of patient safety, verification of regulatory and GCP compliance, verification of IMP supply and facilities and collection of any new documents not provided previously.

Every effort will be made to maintain the anonymity and confidentiality of all subjects during this clinical study. However, because of the experimental nature of this treatment, the investigator agrees to allow the IRB/IEC, representatives of the Sponsor, its designated agents, and authorized employees of the appropriate regulatory agencies to inspect the facilities used in this study and, for purposes of verification, allow direct access to the hospital or clinic records of all subjects enrolled into this study. This includes providing by fax, email, or regular mail de-identified copies of radiology, pathology, and/or laboratory results when requested by the Sponsor. A statement to this effect will be included in the informed consent and permission form authorizing the use of protected health information.

Audits and Inspections

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

7.6 QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor shall implement and maintain quality control and quality assurance

procedures to ensure that the study is conducted, and data are generated, documented, and reported in compliance with the protocol, GCP, and applicable regulatory requirements. This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 2008) and all revisions thereof, and in accordance with FDA regulations (21 CFR Parts 11, 50, 54, 56, and 312, Subpart D – Responsibilities of Sponsors and Investigators) and with the ICH guidelines on GCP (ICH E6).

Any revised protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

AstraZeneca will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO, but the accountability remains with AstraZeneca.

The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR 312.120, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

7.7 DATA HANDLING AND RECORDKEEPING

Subject Screening Log

The investigator must keep a record that lists all subjects considered for enrollment and consented (including those who did not undergo screening) in the study. For those subjects subsequently excluded from enrollment, record the reason(s) for exclusion.

Inspection of Records

The Sponsor or designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

Record Retention

The investigator and other appropriate study staff are responsible for maintaining all documentation relevant to the study. Mandatory documentation includes copies of study protocols and amendments, each FDA Form 1572, IRB/IEC approval letters, signed ICFs, drug accountability records, SAE forms transmitted to the Sponsor, subject files

(source documentation) that substantiate entries in eCRFs, and all relevant correspondence and other documents pertaining to the conduct of the study.

An investigator shall retain records for a period of at least 2 years after the date the last marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. The investigator must notify the Sponsor and obtain written approval from the Sponsor before destroying any clinical study records at any time. The Sponsor will inform the investigator of the date that study records may be destroyed or return to the Sponsor. In accordance with Canadian regulations, all study information collected will be stored for at least 25 years after the end of the study by the study sponsor.

The Sponsor must be notified in advance of, and the Sponsor must provide express written approval of, any change in the maintenance of the foregoing documents if the investigator wishes to move study records to another location or assign responsibility for record retention to another party. If the investigator cannot guarantee the archiving requirements set forth herein at his or her study site for all such documents, special arrangements must be made between the investigator and the Sponsor to store such documents in sealed containers away from the study site so that they can be returned sealed to the investigator for audit purposes.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for a minimum of 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global Retention and Disposal (GRAD) Schedule. No records may be destroyed during the retention period without the written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca.

7.8 PROTOCOL AMENDMENTS

The Sponsor will initiate any change to the protocol in a protocol amendment document. The amendment will be submitted to the IRB/IEC together with, if applicable, a revised model ICF. If the change in any way increases the risk to the subject or changes the scope of the study, then written documentation of IRB/IEC approval must be received by the Sponsor before the amendment may take effect. Additionally, under this circumstance, information on the increased risk and/or change in scope must be provided to subjects already actively participating in the study, and they must read,

understand, and sign any revised ICF confirming willingness to remain in the trial.

7.9 PUBLICATION OF STUDY RESULTS

Authorship, in general, will follow the recommendations of the International Committee of Medical Journal Editors (International Committee of Medical Journal Editors 2014).

7.10 CLINICAL TRIAL INSURANCE

Clinical trial insurance has been obtained according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

7.11 INVESTIGATIONAL STUDY DRUG ACCOUNTABILITY

Acalabrutinib capsules and tablets must be kept in a locked limited access cabinet or space. The study drug must not be used outside the context of this protocol.

Study drug accountability records must be maintained and readily available for inspection by representatives of the Sponsor or regulatory authorities at any time.

Each shipment of study drug will contain a Clinical Supplies Shipping Receipt Form (CSSF). If it is used, the Drug Re-Order Form (provided in the pharmacy binder) must also be included in the site's drug accountability records.

Contents of each shipment must be visually inspected to verify the quantity and to document the condition of study drug capsules and tablets. Following receipt of study drug, the designated recipient completes and signs the CSSF. A copy of the signed and dated CSSF must be faxed or emailed to the Sponsor at the fax number/email address listed on the form; this completed form should be filed in the pharmacy binder.

An Investigational Drug Accountability Log must be used for drug accountability. For accurate accountability, the following information must be noted when drug supplies are used during the study:

1. study identification number (ACE-LY-003)
2. subject identification number
3. lot number(s) of acalabrutinib dispensed for that subject
4. date and quantity of drug dispensed
5. any unused drug returned by the subject

At study initiation, the monitor will evaluate and approve the site's procedure for investigational product disposal/destruction to ensure that it complies with the Sponsor's requirements. If the site cannot meet the Sponsor's requirements for

disposal/destruction, arrangements will be made between the site and the Sponsor or its representative, for return of unused investigational product. Before disposal/destruction, final drug accountability and reconciliation must be performed by the monitor.

All study supplies and associated documentation will be regularly reviewed and verified by the monitor.

7.12 GENERAL INVESTIGATOR RESPONSIBILITIES

The principal investigator must ensure that:

1. He or she will conduct or supervise the study.
2. His or her staff and all persons who assist in the conduct of the study clearly understand their responsibilities and have their names included in the Study Personnel Responsibility/Signature Log.
3. The study is conducted according to the protocol and all applicable regulations.
4. The protection of each subject's rights and welfare is maintained.
5. Signed and dated informed consent and, when applicable, permission to use protected health information are obtained from each subject before conducting study procedures that are not standard of care. If a subject or subject's legal guardian withdraws permission to use protected health information, the investigator will obtain a written request from the subject or subject's legal guardian and will ensure that no further data are collected from the subject.
6. The consent process is conducted in compliance with all applicable regulations and privacy acts.
7. The IRB/IEC complies with applicable regulations and conducts initial and ongoing reviews and approvals of the study.
8. Any amendment to the protocol is submitted promptly to the IRB/IEC.
9. Any significant protocol deviations are reported to the Sponsor and the IRB/IEC according to the guidelines at each study site.
10. eCRF pages are completed promptly.
11. All IND Safety Reports and SUSAR Reports are submitted promptly to the IRB/IEC.
12. All SAEs are reported to the Sponsor's Drug Safety department or designee within 24 hours of knowledge and to the IRB/IEC per their requirements.

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9 APPENDICES

Appendix 1. Performance Status Scores

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

As published in Am J Clin Oncol:

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649–55.

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

Available at: http://www.ecog.org/general/perf_stat.html. Accessed 23 August 2013.

Appendix 2. Adverse Event Assessment of Causality

Is there a reasonable possibility that the event may have been caused by study drug?

No____Yes____

The descriptions provided below will help guide the principal investigator in making the decision to choose either “yes” or “no”:

No = There is no reasonable possibility that the event may have been caused by study drug.

The adverse event:

- may be judged to be due to extraneous causes such as disease or environment or toxic factors
- may be judged to be due to the subject’s clinical state or other therapy being administered
- is not biologically plausible
- does not reappear or worsen when study drug is re-administered
- does not follow a temporal sequence from administration of study drug

Yes = There is a reasonable possibility that the event may have been caused by study drug.

The adverse event:

- follows a temporal sequence from administration of study drug
- is a known response to the study drug based on clinical or nonclinical data
- could not be explained by the known characteristics of the subject’s clinical state, environmental or toxic factors, or other therapy administered to the subject
- disappears or decreases upon cessation or reduction of dose of study drug
- reappears or worsens when study drug is re-administered

Appendix 3. Examples of Coadministered Drugs that Need Additional Consideration

The lists of drugs in these tables are not exhaustive. Any questions about drugs not on this list should be addressed to the medical monitor of this study.

Strong Inhibitors of CYP3A	Moderate inhibitors of CYP3A
boceprevir	aprepitant
clarithromycin [a]	cimetidine
cobicistata	ciprofloxacin
conivaptana	clotrimazole
danoprevir and ritonavir [a,b]	crizotinib,
diltiazema	cyclosporine
elvitegravir and ritonavir [a,b]	dronedaronea
grapefruit juice, Seville oranges, starfruit	erythromycin
idelalisib	fluconazole
indinavir and ritonavir [a,b]	fluvoxamine
Itraconazole [a]	imatinib
Ketoconazole [a]	tofisopam
lopinavir and ritonavir [a,b]	verapamila
nefazodone	
nelfinavira	
paritaprevir and ritonavir [a] and (ombitasvir and/or dasabuvir) [b]	
posaconazole	
ritonavir [a,b]	
saquinavir and ritonavir [a, b]	
telaprevira	
tipranavir and ritonavir [a b]	
troleandomycin	
voriconazole	

a. Inhibitor of P-glycoprotein.

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

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

Strong Inducers of CYP3A
carbamazepine
enzalutamide
mitotane
phenytoin
rifampin
St. John's wort[a]

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

Proton-Pump Inhibitors	H2-Receptor Antagonists
dexlansoprazole	cimetidine
esomeprazole	famotidine
lansoprazole	nizatidine
omeprazole	ranitidine
rabeprazole	
pantoprazole	

Source: FDA Established Pharmacologic Class Text Phrase. Web link accessed 18 July 2018: https://www.fda.gov/downloads/drugs/guidancecompliance regulatoryinformation/lawsactsandrules/ucm428333.pdf

Appendix 4. Schedule of Assessments Part 1

	Screening[a]	Cycle 1				Cycle 2		Cycle 3	Cycles 4-6	Cycle 7	Cycles 8-12[b]	Cycle ≥13[c]	Safety Follow-Up[d]	LTFU[e]
		Day	Days (±2)			Days (±2)		Days (±2)	Days (±2)	Days (±2)	Days (±2)	Days (±7)	Days (+7)	
		1	8	15	22	1	15	1	1	1	1	1		
Informed consent	x													
Confirm eligibility	x													
Medical history	x													
PE[f]/Vital signs[g]/Weight	x	x	x	x	x	x	x	x	x	x	x	x	x	
ECOG status	x	x	x	x	x	x	x	x	x	x	x	x	x	
ECG[h]	x												x	
Lab assessments:														
Serum or urine pregnancy[i]	x												x	
Hematology[j]	x	x[k]	x	x	x	x	x	x	x	x	x	x	x	
Serum chemistry[l]	x	x[k]	x	x	x	x	x	x	x	x	x	x	x	
Hepatitis serology[m]	x													
HBV PCR[n]	x					x		x	x	x	x	x	x	x
HCV PCR[n]	x													
Urinalysis[o]	x													
T/B/NK cell count[p]		x[k]						x		x				
Serum Ig[q]		x[k]						x		x			x	
Bone marrow (aspirate/biopsy)[r]	x							to confirm CR (if bone marrow was involved by lymphoma at baseline)						
Pharmacodynamics		x[m]	x[m]			x[n]		x[n]					x	
Pharmacokinetics[u]		x	x	x	x	x								
Acalabrutinib dispensed		x				x		x	x	x	x	x		
Rituximab administered[v]		x	x	x	x	x		x	x					
Study drug compliance		x	x	x	x	x	x	x	x	x	x	x		
Tumor assessment[r]	x	x	x	x	x	x	x	x	x	x	x	x		
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	
Adverse events[w]		x	x	x	x	x	x	x	x	x	x	x	x	
Time-to-next treatment														x

anti-HBc=hepatitis B core antibodies; anti-HBs=hepatitis B surface antibody; CR=complete remission; CT=computed tomography; ECOG=Eastern Cooperative Oncology Group, FL=follicular lymphoma; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; Ig=immunoglobulin; IVIG=intravenous immunoglobulin; LTFU=long-term follow-up; PCR=polymerase chain reaction; PE=physical examination; PET=positron-emission tomography; T/B/NK=T cell/B cell/natural killer.

a. Screening tests should be performed within 21 days before the first administration of study drug, unless otherwise indicated.
b. Treatment with acalabrutinib may be continued until disease progression or an unacceptable drug-related toxicity occurs as defined in the protocol. The end of the study is defined as the final data cut-off for the final analysis (Section 3.2).
c. Study assessments (including clinical evaluations, laboratories, and CT) are required on Day 1 of Cycle 13 and every 3 cycles thereafter (i.e., Cycles 16, 19, etc.).
d. Until the final data cut-off, a 30-day (+7 days) safety follow-up visit is required when subjects discontinue study drug.
e. Subjects who discontinue study therapy will continue on study for long-term follow-up of time-to-next therapy for FL (every 8-12 weeks) unless they withdraw consent for further follow-up.
f. The physical examination includes height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities,

musculoskeletal, nervous, lymphatic system, and general appearance. The lymphatic system examination will include examination of palpable lymph nodes and spleen and liver below the costal margin on the respective side. Only physicians, physician assistants, or oncology nurse practitioners should perform the lymphatic system examination. As much as possible, the same person should perform all the lymphatic exams for a given subject.

g. Vital signs (blood pressure, pulse, respiratory rate, and temperature) will be assessed after the subject has rested in the sitting position.
h. Subjects should be in supine position and resting for ≥10 minutes before study-related ECGs. A 12-lead ECG will be performed in triplicate (≥1 minute apart) at screening. The calculated QTc average of the 3 ECGs must be ≤480 ms for eligibility. If results from an unscheduled ECG are abnormal and considered clinically significant at any time, then an electrolyte panel (i.e., calcium, magnesium, and potassium) must be obtained to coincide with the ECG testing.
i. Women of childbearing potential only.
j. Hematology includes complete blood count with differential and platelet counts. Cycle 1 Day 1 hematology does not need to be repeated if screening hematology was within 5 days.
k. The indicated samples at this timepoint (Cycle 1 Day 1) must be drawn predose.
l. Serum chemistry: albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen, bone-specific alkaline phosphatase, calcium, chloride, creatinine, glucose, LDH, magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid. Cycle 1 Day 1 serum chemistry does not need to be repeated if screening serum chemistry was within 5 days.
m. Hepatitis serology must include HBsAg, anti-HBs, anti-HBc, and HCV antibody. In addition, any subjects testing positive for anti-HBc or HVC antibody, must have additional PCR testing during screening (see Section 4.1.14). Subjects who are receiving prophylactic IVIG and have positive HBsAg or anti-HBc must have negative hepatitis B DNA to be eligible. Those who are HBsAg positive or hepatitis B PCR positive and those who are hepatitis C PCR positive will be excluded.
n. Subjects who are anti-HBc positive (or have a known history of HBV infection) should have PCR testing for HBV DNA performed during screening and monthly thereafter. Monthly monitoring should continue until 12 months after last dose of study drug. Any subject with a rising viral load (above lower limit of detection) should discontinue study drug(s) and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B. If the HBV DNA PCR is needed during long-term follow-up, it can be performed at a local laboratory. Subjects with a known history of hepatitis C or who are hepatitis C antibody positive should be tested by quantitative PCR for HCV RNA during screening. Such subjects may be enrolled provided the quantitative PCR is negative (undetectable viral load). No further monitoring for HCV RNA during treatment is necessary if initial PCR results are negative.
o. Urinalysis: pH, ketones, specific gravity, bilirubin, protein, blood, and glucose.
p. T/B/NK cell count (i.e., $CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, $CD16^+/56^+$).
q. Serum immunoglobulin: IgG, IgM, IgA.
r A pretreatment CT scan with contrast (unless contraindicated) is required of the chest, abdomen, and pelvis and any other disease sites (e.g., neck) within 30 days before the first dose of study drug. A pretreatment PET/CT scan within 60 days before the first dose of study drug. During treatment, CT scans will be performed for tumor assessments on Day 1 of Cycle 3 (±7 days), Cycle 5 (±7 days), Cycle 7 (±7 days); and then every 3 cycles (12 weeks, ±7 days) thereafter (i.e., Cycles 10, 13, 16, etc.) up to 2 years then every 6 cycles (24 weeks) or more frequently at the investigator's discretion. Bone marrow (if bone marrow was involved by lymphoma at baseline) and PET/CT are required to confirm CR per clinical guidelines (see Section 4.2). When possible, extra bone marrow tissue may be used for pharmacodynamic evaluation. At all other visits, tumor assessments will be performed by physical examination and laboratory results.
s. Pharmacodynamic samples are drawn predose and 4 hours (±10 minutes) postdose on the days indicated. Timepoints are relative to the morning dose.
t. Pharmacodynamic samples are drawn predose on the days indicated.
u. Pharmacokinetic samples are drawn per Table 4.
v. Rituximab 375 mg/m^2 IV on Days 1, 8, 15 and 22 of Cycle 1 and Day 1 of Cycles 2 through 6.
w. After the end of the protocol-defined adverse event reporting period (see Section 6.3.1), only serious adverse events considered related to study drug(s) or study procedures are required to be collected.

Appendix 5. Schedule of Assessments Part 2

	Screening[a]	Cycle 1				Cycle 2		Cycle 3	Cycles 4-6	Cycle 7	Cycles 8-12[b]	Cycles ≥13[c]	End of treat-ment	Safety Follow -up[d]	DFU[e]	LTFU[f]
		Day	Days (± 2)			Days (± 2)		Days (± 2)	Days (± 2)	Days (± 2)	Days (± 2)	Days (± 7)	Days (± 7)	Days (+ 7)	Days (± 7)	Days (± 7)
		1	8	15	22	1	15	1	1	1	1	1				
Informed consent	x															
Confirm eligibility	x															
Medical history	x															
PE[g]/Vital signs[h]/Weight	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
ECOG status	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
ECG[f]	x												x	x		
Endoscopy (gastric MALT)[j]	x								to confirm CR							
Lab assessments:																
Serum or urine pregnancy[k]	x	x				x		x	x	x	x	x	x	x		
Hematology[l]	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Serum chemistry[m]	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Hepatitis serology[n]	x															
HBV PCR[n]	x					x		x	x	x	x	x		x	x	x
HCV PCR[n]	x															
Urinalysis[o]	x															
T/B/NK cell count[p]		x[q]						x		x			x			
Serum Ig[r]		x[q]						x		x				x		
Bone marrow (aspirate/biopsy)[j]	x								to confirm CR (if bone marrow was involved by lymphoma at baseline), optional at end of treatment							
Pharmacodynamics[s]		x				x		x					x			
^{13}C urea breath test (gastric MALT)[t]	x															
Acalabrutinib dispensed[u]		x				x		x	x	x	x	x				
Rituximab administered[v]		x	x	x	x	x		x	x							
Study drug compliance		x	x	x	x	x	x	x	x	x	x	x	x			
Tumor assessment[j]	x	x	x	x	x	x	x	x	x	x	x	x			x	
Archival tumor[w]	x															
Peripheral blood for MRD[w]								Within 12 weeks of confirmation of radiological CR or PR					x			
Time-to-next treatment															x[e]	x[f]

	Screening[a]	Cycle 1				Cycle 2		Cycle 3	Cycles 4-6	Cycle 7	Cycles 8-12[b]	Cycles ≥13[c]	End of treat-ment	Safety Follow -up[d]	DFU[e]	LTFU[f]
		Day	Days (± 2)			Days (± 2)		Days (± 2)	Days (± 2)	Days (± 2)	Days (± 2)	Days (± 7)	Days (± 7)	Days (+ 7)	Days (± 7)	Days (± 7)
		1	8	15	22	1	15	1	1	1	1	1				
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Adverse events[x]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Overall survival																x

anti-HBc=hepatitis B core antibodies; anti-HBs=hepatitis B surface antibody; CR=complete remission; CT=computed tomography; DFU=disease follow-up; ECOG=Eastern Cooperative Oncology Group; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; Ig=immunoglobulin; IVIG=intravenous immunoglobulin; LTFU=long-term follow-up; MALT=mucosa-associated lymphoid tissue; MRD=minimum residual disease; PCR=polymerase chain reaction; PE=physical examination; PET=positron-emission tomography; PR=partial response; T/B/NK=T cell/B cell/natural killer.

a. Screening tests should be performed within 28 days before the first administration of study drug, unless otherwise indicated.
b. Treatment with acalabrutinib may be continued until disease progression or an unacceptable drug-related toxicity occurs as defined in the protocol. The end of the study is defined as the final data cut-off for the final analysis (Section 3.2).
c. Study assessments (including clinical evaluations, laboratories, and CT) are required on Day 1 of Cycle 13 and every 3 cycles for clinical visit and every 6 cycles for CT scan thereafter.
d. Until the final data cut-off, a 30-day (+ 7 days) safety follow-up visit is required for **all** subjects after his or her last dose of study drug to monitor for adverse events to document the occurrence of any new events, regardless of whether the subject receives a new anticancer therapy or demonstrates disease progression within this timeframe.
e. Subjects who discontinue for reasons other than progressive disease will be followed for disease progression (via CT scans per investigator discretion), regardless of whether the subjects receive a new anticancer therapy. The time-to-next treatment information will also be collected. Subjects will then continue long-term follow-up (Section 4.4).
f. Once subjects discontinue due to disease progression regardless of whether disease progression occurred during the study treatment period or disease follow-up period, they will be contacted approximately every 12 weeks by clinic visit or telephone, to obtain the information for the time to start of alternative anticancer therapy and assess survival until the subject dies, is lost to follow-up, or withdraws consent.
g. The physical examination includes height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal, nervous, lymphatic system, and general appearance. The lymphatic system examination will include examination of palpable lymph nodes and spleen and liver below the costal margin on the respective side. Only physicians, physician assistants, or oncology nurse practitioners should perform the lymphatic system examination. As much as possible, the same person should perform all the lymphatic exams for a given subject.
h. Vital signs (blood pressure, pulse, respiratory rate, and temperature) will be assessed after the subject has rested in the sitting position.
i. Subjects should be in supine position and resting for ≥10 minutes before study-related ECGs. A 12-lead ECG will be performed in triplicate (≥1 minute apart) at screening. The calculated QTcF average of the 3 ECGs must be ≤480 ms for eligibility. If results from an unscheduled ECG are abnormal and considered clinically significant at any time, then an electrolyte panel (i.e., calcium, magnesium, and potassium) must be obtained to coincide with the ECG testing.
j. Tumor assessments: 1) An endoscopy for subjects with gastric MALT lymphoma is required within 90 days before the dose of study drug. 2) A pretreatment CT scan with contrast (unless contraindicated) is required of the chest, abdomen, and pelvis and any other disease sites (e.g., neck) within 30 days before the first dose of study drug. A pretreatment PET/CT scan within 60 days before the first dose of study drug. During treatment, CT scans will be performed for tumor assessments every 3 cycles (12 weeks, ±7 days) starting at Day 1 of Cycle 4, Cycle 7, Cycle 10, and Cycle 13, and then every 24 weeks thereafter or more frequently at the investigator's discretion. 3) A bone marrow aspirate/biopsy is required within 90 days before the first dose of study drug and is optional at the end of treatment for molecular profiling to discover mechanisms of resistance to study treatment. Bone marrow aspirate/biopsy (if involved by lymphoma at baseline), endoscopy (for subjects with gastric MALT), and PET/CT to confirm CR per clinical guidelines (see Section 4.2). When possible, extra bone marrow tissue may be used for pharmacodynamic evaluation. 4) At all other visits, tumor assessments will be performed by physical examination and laboratory test results.
k. Women of childbearing potential only on Day 1 of each cycle.
l. Hematology includes complete blood count with differential and platelet counts. Cycle 1 Day 1 hematology does not need to be repeated if screening hematology was within 5 days.
m. Serum chemistry: Albumin, alkaline phosphatase, alanine transaminase, aspartate aminotransferase, bicarbonate, blood urea nitrogen, bone-specific alkaline phosphatase, calcium, chloride, creatinine, glucose, lactate dehydrogenase, magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid. Cycle 1 Day 1 serum chemistry does not need to be repeated if screening serum chemistry was within 5 days.

n. Hepatitis serology must include HBsAg, anti-HBs, anti-HBc, and HCV antibody. Subjects who are anti-HBc positive should have PCR testing for HBV DNA performed during screening and monthly 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. Subjects with a known history of hepatitis C or who are hepatitis C antibody positive should be tested by quantitative PCR for HCV RNA during screening. Such subjects may be enrolled provided the quantitative PCR is negative (undetectable viral load). No further testing beyond screening is necessary if PCR results are negative.
o. Urinalysis: pH, ketones, specific gravity, bilirubin, protein, blood, and glucose.
p. T/B/NK cell count (i.e., $CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, $CD16^+/56^+$).
q. The indicated samples at this timepoint (Cycle 1 Day 1) must be drawn predose.
r Serum immunoglobulin: IgG, IgM, IgA.
s. Pharmacodynamic samples are drawn predose.
t. A ^{13}C urea breath test will be performed at screening only if the subject does not have H. pylori results from a pathology report. If this test is needed, proton-pump inhibitors and H2 blockers must be discontinued or withheld 14 days and 7 days, respectively, and antibiotics for treating H. pylori, such as those with anti-helicobacter action and bismuth preparations, should be withheld at least 30 days before the test.
u. Subjects will receive their supply of acalabrutinib in the clinic on Day 1 of Cycle 1 and Cycle 2, and Day 1 of subsequent scheduled visits. Subjects should take their acalabrutinib dose in the clinic on Day 1 of Cycle 1. For treatments taken in the clinic, subjects should take acalabrutinib from the drug dispensed for that particular time period. All other acalabrutinib treatments will be taken at home.
v. Rituximab 375 mg/m^2 intravenously on Days 1, 8, 15, and 22 of Cycle 1 and Day 1 of Cycles 2 through 6. On the day when rituximab is administered, acalabrutinib will be administered first and rituximab will be administered approximately1 hour after the acalabrutinib dose.
w. Archival tumor sample are collected for baseline genomics and MRD. For subjects with involved bone marrow, a bone marrow biopsy is acceptable. Molecular profiling and MRD testing will be performed on tumor biopsy, peripheral blood samples, and bone marrow samples by a central laboratory. A blood sample is to be collected within 12 weeks for subjects with radiological confirmation of CR or PR and at the end of treatment visit for subjects who discontinue study treatment for any reason. For subjects with lymphoma involvement of bone marrow at baseline, the bone marrow biopsy performed for CR confirmation should also be collected for MRD evaluation.
x. After the end of the protocol-defined adverse event reporting period (see Section 6.3.1), only serious adverse events considered related to study drug(s) or study procedures are required to be collected.

Appendix 6. Schedule of Assessments Part 3

	Screening[a]	Cycle 1				Cycle 2		Cycle 3	Cycles 4-6	Cycle 7	Cycles 8-12[b]	Cycles 13[c]-27	Cycle ≥ 28 (Q3M)	End of treat-ment	Safety Follow -up[d]	DFU[e]	LTFU[f]
		Day	Days (± 2)					Days (± 2)	Days (± 2)	Days (± 2)	Days (± 2)	Days (± 2)	Days (± 7)	Days (± 7)	Days (+ 7)	Days (± 7)	Days (± 7)
		1	8	15	22	1	15	1	1	1	1	1	1				
Informed consent	x																
Confirm eligibility	x																
Medical history	x																
PE[g]/Vital signs[h]/Weight	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
ECOG status	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
ECG[i]	x													x	x		
Lab assessments:																	
Serum or urine pregnancy[j]	x[j]	x	x	x	x	x		x	x	x	x	x	x	x	x		
Hematology[k]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Serum chemistry[l]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Hepatitis serology[m]	x																
HBV PCR[m]	x					x		x	x	x	x	x	x		x	x	x
HCV PCR[m]	x																
Urinalysis[n]	x																
T/B/NK cell count[o]		x						x		x				x			
Serum Ig[p]		x						x		x					x		
Bone marrow (aspirate/ biopsy)[q,r]	x								to confirm CR and for MRD (if bone marrow was involved by lymphoma at baseline), optional at end of treatment								
TSH, T3, T4	x								Every 12 weeks during treatment with lenalidomide and 12 weeks after the last dose of lenalidomide								
Pharmacodynamics		x[s]	x[s]			x[s]		x[s]						x[s]			
Pharmacokinetics		x[s]	x[s]			x[s]											
Acalabrutinib dispensed[t]		x				x		x	x	x	x	x	x				
Enroll in REVLIMID REMS[u]	x																
Lenalidomide dispensed[v]		x				x		x	x	x	x						
Rituximab administered[w]		x	x	x	x	x		x	x		x	x					

Study drug compliance		x	x	x	x	x	x	x	x	x	x	x	x	x			
Tumor assessment[q]	x	x	x	x	x	x	x	x	x	x	x	x	x			x	
Archival tumor[x]	x																
Peripheral blood for baseline molecular profile[y]	x																
Peripheral blood for ctDNA[z]	x								x	x	x	x	x	x			
Saliva sample for ctDNA[z]	x																
Peripheral blood for MRD[r]								Within 12 weeks of confirmation of radiological CR or PR									
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Adverse events[aa]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	

anti-HBc=hepatitis B core antibodies; anti-HBs=hepatitis B surface antibody; CR=complete remission; CT=computed tomography; ctDNA=circulating tumor DNA; DFU=disease follow-up, ECOG=Eastern Cooperative Oncology Group, HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; Ig=immunoglobulin; IVIG=intravenous immunoglobulin; LTFU=long-term follow-up; MRD=minimum residual disease; PCR=polymerase chain reaction; PE=physical examination; PET=positron-emission tomography; PR=partial response; Q3M=every 3 months; SFU=safety follow-up; T3=triiodothyroxine; T4=thyroxine; T/B/NK=T cell/B cell/natural killer; TSH=thyroid stimulating hormone.

a. Screening tests should be performed within 28 days before the first administration of study drug, unless otherwise indicated.
b. Treatment with acalabrutinib may be continued until disease progression or an unacceptable drug-related toxicity occurs as defined in the protocol. The end of the study is defined as the final data cut-off for the final analysis (Section 3.2).
c. Study assessments (including clinical evaluations, laboratories, and CT) are required on Day 1 of Cycle 13 and every 3 cycles for the clinical visit and every 6 cycles for CT scan thereafter. (Pregnancy testing for women of childbearing potential will still be required monthly).
d. Until the final data cut-off, a 30-day (+7 days) safety follow-up visit is required for **all** subjects after his or her last dose of study drug to monitor for adverse events to document the occurrence of any new events, regardless of whether the subject receives a new anticancer therapy or demonstrates disease progression within this timeframe.
e. Each subject should be followed until disease progression or the start of alternative anticancer therapy. If neither of these has occurred at the time of the 30-day SFU visit, DFU visits should occur approximately every 12 weeks until disease progression or next anticancer treatment. During this period, subjects will be followed via CT scans.
f Once subjects discontinue due to disease progression regardless of whether disease progression occurred during the study treatment period or disease follow-up period, they will be contacted approximately every 12 weeks by clinic visit or telephone, to obtain the information for the time to start of alternative anticancer therapy and assess survival until the subject dies, is lost to follow-up, or withdraws consent.
g. Physical examination includes height (Screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal, nervous, lymphatic system, and general appearance. The lymphatic system examination will include examination of palpable lymph nodes and spleen and spleen and liver below the costal margin on the respective side. Only physicians, physician assistant, or oncology nurse practitioners should perform the lymphatic system examination. As much as possible, the same person should perform all the lymphatic exams for a given subject.
h. Vital sign measurements (blood pressure, pulse, respiratory rate, and body temperature) will be assessed after the subject has rested in the sitting position.
i. Subjects should be in supine position and resting for ≥10 minutes before study-related ECGs. A 12-lead ECG will be performed in triplicate (≥1 minute apart) at screening. The calculated QTcF average of the 3 ECGs must be ≤480 ms for eligibility. If results from an unscheduled ECG are abnormal and considered clinically significant at any time, then an electrolyte panel (i.e., calcium, magnesium, and potassium) must be obtained to coincide with the ECG testing.
j. Women of childbearing potential must have two negative pregnancy tests prior to the first dose of lenalidomide. The first pregnancy test should be performed 10 to 14 days before the first dose and the second test within 24 hours prior to the first dose of lenalidomide. Pregnancy tests should be performed weekly in the first month and then monthly thereafter until 4 weeks after discontinuation of lenalidomide.
k. Hematology includes complete blood count with differential and platelet counts. Cycle 1 Day 1 hematology does not need to be repeated if screening hematology was within 5 days.
l. Serum chemistry: Albumin, alkaline phosphatase, alanine transaminase, aspartate aminotransferase, bicarbonate, blood urea nitrogen, bone-specific alkaline phosphatase, calcium, chloride, creatinine, glucose, lactate dehydrogenase, magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid. Only at

baseline: Creatinine clearance >60 mL/min. Cycle 1 Day 1 serum chemistry does not need to be repeated if screening serum chemistry was within 5 days.

m. Hepatitis serology must include HBsAg, anti-HBs, anti-HBc, and HCV antibody. Subjects who are anti-HBc positive should have PCR testing for HBV DNA performed during screening and monthly 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. Subjects with a known history of hepatitis C or who are hepatitis C antibody positive should be tested for HCV RNA during screening. No further testing beyond screening is necessary if PCR results are negative.
n. Urinalysis: pH, ketones, specific gravity, bilirubin, protein, blood, and glucose. Cycle 1 Day 1 urinalysis does not need to be repeated if screening urinalysis was within 5 days.
o. T/B/NK cell count (i.e., $CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, $CD16^+/56^+$).
p. Serum immunoglobulin: IgG, IgM, IgA.
q. Tumor assessments: 1) A pretreatment CT scan with contrast (unless contraindicated) is required of the chest, abdomen, and pelvis and any other disease sites (e.g., neck) within 30 days before the first dose of study drug. 2) A pretreatment PET/CT scan within 60 days before the first dose of study drug is required. During treatment, PET/CT scans will be performed at Cycle 4 Day 1 (Week 12), Cycle 7 Day 1 (Week 24), and at CR. CT scans will be performed for tumor assessments every 3 cycles (12 weeks, ±7 days) starting at Day 1 of Cycle 4, Cycle 7, Cycle 10, and Cycle 13, then every 24 weeks thereafter or more frequently at the investigator's discretion. 3) A bone marrow aspirate/biopsy is required within 90 days before the first dose of study drug. 4) To confirm CR, PET/CT must be performed and, if bone marrow was involved by lymphoma at baseline, a bone marrow aspirate/biopsy must be performed (see Section 4.1.8). 5) At all other visits, tumor assessments will be performed by physical examination.
r. Molecular profiling and MRD testing will be performed on tumor biopsy, peripheral blood samples, and bone marrow samples by a central laboratory. 1) A blood sample is to be collected within 12 weeks for subjects with radiological confirmation of CR or PR and at the end of treatment visit for subjects who discontinue study treatment for any reason. 2) For subjects with lymphoma involvement of bone marrow at baseline, a bone marrow biopsy performed for CR confirmation and a bone marrow aspirate should also be collected for MRD evaluation.3) Baseline evaluation of MRD will be based on archival lymph node biopsy or bone marrow biopsy for subjects with involved bone marrow, or tissue sample obtained at screening.
s. Pharmacodynamic samples will be drawn for Cycle 1 Day 1 (predose and 4 hours postdose) and on Cycle 1 Day 8 (predose and 4 hours postdose). Pharmacodynamic samples will be taken predose on Cycle 2 Day 1, Cycle 3 Day 1, at disease progression, and at EOT. Pharmacokinetic samples will be drawn for Cycle 1 Day 1 and Day 8, and Cycle 2 Day 1 at 1 and 4 hours postdose of acalabrutinib.
t. Subjects will receive their supply of acalabrutinib in the clinic on Day 1 of Cycle 1 and Cycle 2, and Day 1 of subsequent scheduled visits. Subjects should take their acalabrutinib dose in the clinic on Day 1 of Cycle 1. For treatments taken in the clinic, subjects should take acalabrutinib from the drug dispensed for that particular time period. All other acalabrutinib treatments will be taken at home.
u. Lenalidomide is available only under a special restricted program called REVLIMID REMS to avoid fetal exposure because of potential toxicity. Prescribers and pharmacists registered with the program can prescribe and dispense the product to subjects who are registered and meet all the conditions of the REVLIMID REMS program. All subjects (males and females) receiving lenalidomide must be enrolled in the REVLIMID REMS program.
v. Lenalidomide is to be taken orally daily on Days 1 through 21 of each cycle for up to 12 cycles or until disease progression or intolerance, whichever comes first. The starting dose is 15 mg QD and the final dose for dose expansion will be based on DLT evaluation. On days that both acalabrutinib and lenalidomide are administered, lenalidomide should be taken approximately 30 minutes prior to the first daily dose of acalabrutinib. Please note that on PK sample collection days, the time of dosing for all study drugs must be recorded in the clinical database (electronic case report form).
w. Rituximab 375 mg/m^2 IV administered on Days 1, 8, 15, and 22 of Cycle 1, and Day 1 of every cycle starting at Cycle 2 through Cycle 6, followed by 10 additional doses of maintenance rituximab every other cycle beginning with Cycle 8 for subjects who have not progressed. On the day when rituximab is administered, acalabrutinib will be administered first and rituximab will be administered approximately 1 hour later. After the last Rituximab dose on Cycle 26, then visits are to occur every 3 cycles starting on Cycle 28 until disease progression or intolerance.
x. Archival tumor sample are collected for baseline genomics and MRD. For subjects with disease involved bone marrow, a bone marrow biopsy is acceptable.
y. Baseline peripheral blood sample will be drawn for molecular profiling using genomics.
z. ctDNA samples will be collected at screening and, at every tumor assessment visit beginning with Cycle 4 and at end of treatment. A 2-mL saliva sample to serve as a matched normal control sample will be collected.
aa. After the end of the protocol-defined adverse event reporting period (see Section 6.3.1, only serious adverse events considered related to study drug(s) or study procedures are required to be collected.

Appendix 7. Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

INTRODUCTION

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

During the course of the study, the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a subject meets PHL criteria at any point during the study. All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits, including central and all local laboratory evaluations, even if collected outside of the study visits (e.g., PHL criteria could be met by an elevated ALT from a central laboratory and/or elevated total bilirubin from a local laboratory). The investigator will also review adverse event (AE) data (e.g., for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The investigator participates with the sponsor in the review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury (DILI) caused by the investigational medicinal product (IMP). The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting AEs and serious adverse events (SAEs) according to the outcome of the review and assessment in line with standard safety-reporting processes.

DEFINITIONS

Potential Hy's Law

AST or ALT ≥3 x ULN together with total bilirubin ≥2 x ULN at any point during the study after the start of study drug, irrespective of an increase in alkaline phosphatase.

Hy's Law

AST or ALT ≥3 x ULN together with total bilirubin ≥2 x ULN, where no reason other than the IMP can be found to explain the combination of increases (e.g., elevated alkaline phosphatase indicating cholestasis, viral hepatitis, or another drug).

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

IDENTIFICATION OF POTENTIAL HY'S LAW CASES

Laboratory data must be comprehensively reviewed by the investigator for each subject to identify laboratory values meeting the following criteria:

- ALT ≥3 x ULN
- AST ≥3 x ULN
- Total bilirubin ≥2 x ULN

When the identification criteria are met from central or local laboratory results, the investigator will perform the following:

- Notify the sponsor representative/Medical Monitor by telephone and report the PHL case as an SAE of Potential Hy's law: seriousness criteria "Important medical event" and causality assessment "yes/related" or in accordance with the clinical study protocol as appropriate.
- Request a repeat of the test (new blood draw) without delay
- Complete the appropriate unscheduled laboratory electronic Case Report Form (eCRF) module(s)
- Perform follow-up on subsequent laboratory results according to the guidance provided in the clinical study protocol, as applicable

REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

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

As soon as possible after the biochemistry abnormality is initially detected, the study Medical Monitor and the Investigator will review available data, to agree whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP and to ensure that timely analysis and reporting to health authorities within 15 calendar days from the date PHL criteria were met.

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

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

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

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

If there is an unavoidable delay of over 15 calendar days in obtaining the information necessary to assess whether the case meets the criteria for HL, then it is assumed that there is no alternative explanation until an informed decision can be made:

- Provide any further update to the previously submitted SAE of PHL (report term now "Hy's law case"), ensuring causality assessment is related to IMP and seriousness criteria are medically important, according to clinical study protocol process.
- Continue follow-up and review according to the agreed plan. After the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following the clinical study protocol process, according to the outcome of the review.

ACTIONS REQUIRED FOR REPEAT EPISODES OF POTENTIAL HY'S LAW

This section is applicable when a subject meets PHL criteria while receiving study treatment and has already met PHL criteria at a previous on-study treatment visit. The

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

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

Was the alternative cause for the previous occurrence of PHL determined to be the disease under study (e.g., chronic or progressing malignant disease, severe infection, or liver disease)?

- If the answer is **No:**

  Follow the process described in "Potential Hy's Law Criteria Met" in this Appendix for reporting PHL as an SAE.

- If the answer is **Yes**:

  Determine whether there has been a significant change in the subject's condition compared with the previous occurrence of PHL. Note: A "significant" change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator; this may be in consultation with the study medical monitor if there is any uncertainty.

  - If there is no significant change, no action is required.
  - If there is a significant change, follow the process described in "Potential Hy's Law Criteria Met" in this Appendix for reporting PHL as an SAE.

LABORATORY TESTS

The list below represents a comprehensive list of follow-up tests that may aid in assessing PHL/HL.

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

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR

Viral hepatitis	IgM anti-HAV IgM and IgG anti-HBc HBsAg HBV DNA IgM and IgG anti-HCV HCV RNA IgM anti-HEV HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin)
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin Transferrin saturation

Reference

FDA Guidance for Industry (issued July 2009). Drug-induced liver injury: Premarketing clinical evaluation
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Appendix 8. Management of Study Procedures During Pandemic

This appendix consolidates guidance for subject safety and ongoing access to medical care and investigational product during the global COVID-19 pandemic. The measures detailed below will be implemented across the Sponsor studies on a temporary basis until the pandemic is considered resolved by governmental and public health organizations, as applicable.

Regardless of the guidance below, please consider public health advice in your local market and individual risk/benefit in treatment decisions for patients at your study site during the pandemic. Please also consider logistical requirements such as the ability of patients to travel to the study site, accessibility of public transport, etc.

If the subject is unable or unwilling to visit the study site due to COVID-19 related reasons, investigators may ask enrolled subjects to use healthcare facilities local to the subject to ensure safety and efficacy measures are done per protocol. If a study assessment is not done at either the site or a facility local to the subject, then its absence should be documented as a protocol deviation. Any protocol deviations resulting from the COVID-19 situation should be recorded and prefixed with COVID-19.

STUDY SUBJECT PARTICIPATION

Conduct of Telephone Visits

Due to the current pandemic, it is conceivable that not all subject visit commitments may be able to be fulfilled. If a subject is unable or unwilling to attend a study visit, adaptation of the onsite visit to a telephone visit is recommended to ensure continuity of study care (as an interim measure; e.g., telephone contacts instead of visits, shipping study medication to the subject). Priority should be given to maintaining ongoing safety follow-up (even if this is conducted by telephone contacts). Study sites should speak with their site monitor before performing a telephone visit so he or she may provide guidance regarding logistics that may need consideration. Also, study sites should speak with the site monitor if the subject cannot attend more than one onsite visit in succession, because multiple incomplete visits may have the potential to impact evaluation of study endpoints.

Acalabrutinib Dose Modification Recommendation for COVID-19

The Sponsor recognizes that coronavirus 2019-nCoV (COVID-19) presents an increased risk for all patients. Due to the potential impact of COVID-19 on multiple organ systems, the Sponsor recommends the following dose modification and management plan for patients with confirmed or suspected COVID-19 while receiving treatment with

acalabrutinib.

First and foremost, the following safety reporting guidelines are required:

All confirmed or suspected COVID-19-related adverse events (AEs) must be recorded in the eCRF. All dose modifications should be based on the worst Common Terminology Criteria for Adverse Events (CTCAE) grade. All interruptions or modifications must be recorded on the AE and drug administration eCRFs. The CTCAE general grading criteria should be used to evaluate COVID-19.

If an event is suspected to be COVID -19 infection, the Sponsor recommends interrupting acalabrutinib and testing for COVID-19 per local guidance.

- If COVID-19 is ruled out, standard clinical practice and the study protocol procedures should be followed regarding any dose modifications required for management of severe infections.
- If COVID-19 is confirmed or diagnosis is suspected after evaluation, COVID-19 infection should be managed per local guidance until the subject achieves full recovery, defined as no signs or symptoms.

In case of COVID-19 positivity, the investigator must determine the risk and benefit of interruption versus continuation of acalabrutinib and whether to resume it at full or modified doses or discontinue treatment.

Please contact the study medical monitor for further discussion.

Comparator Drugs or Drugs used in Combination with Acalabrutinib

- Please refer to guidance from the manufacturer.

Drug-drug interactions (DDI) may occur with some of the drugs being used as best supportive care (e.g., drugs that are strong inducers or inhibitors of cytochrome P450 [CYP]3A). Guidance is provided below:

Drug-Drug Interaction Guidance for Investigators with Subjects Enrolled in an Acalabrutinib Clinical Study Who Are COVID-19 Positive

- The potential combination with chloroquine or 8-8-OH-chloroquine (8-OH-CHQ) and azithromycin are not predicted to have a pharmacokinetic DDI with acalabrutinib. However, both agents are known to cause cardiovascular risk of QT prolongation. Therefore, the risk/benefit of initiating 8-OH-CHQ + azithromycin should be discussed with the medical monitor.

- Many antivirals and antibiotics are considered strong CYP3A4 inhibitors or inducers and are therefore likely to cause complex DDIs with acalabrutinib. The risk benefit balance of acalabrutinib use in the setting of COVID-19 treatment should be discussed between the investigator and the medical monitor.
- Remdesivir is rapidly metabolized to a pharmacologically active metabolite, GS-443902. Based on published and publicly available data, remdesivir does not appear to inhibit CYP isoforms and will likely not interact in a meaningful way with drug transport systems. Remdesivir does not prolong QTc interval.
- Systemic steroids and acalabrutinib may impair the ability of the body to fight infection; it is best to avoid high-dose systemic steroids while taking acalabrutinib.
- The study protocol and investigator brochure should be referenced for other DDI information.

COVID-19 SPECIFIC DATA ENTRY INSTRUCTIONS FOR INVESTIGATIONAL SITES

Adverse Event Recording

Currently no changes to normal data capture procedures are required for COVID-19 data in the eCRF. For subjects who have confirmed or who are suspected of having coronavirus infection, the infection should be documented as an AE or serious adverse event (SAE), in line with instructions for safety reporting documented in the clinical study protocol. Either **"COVID 19 Confirmed" or "COVID-19 Suspected"** should be used when reporting the event as follows:

- If test is positive, "COVID-19 confirmed" should be recorded in the AE field.
- If test is negative, AE/SAE signs and symptoms and/or other diagnosis should be recorded in the AE field(s).
- If test is not available and signs and symptoms, as judged by the investigator, are highly suspicious of COVID-19 infection, record "COVID-19 suspected" in the AE field.

Details of any testing or procedure to determine the status of COVID-19 infection should be documented on the Concomitant Procedure Form if available or on the appropriate eCRF page in the study.

For fatal SAEs, the Death Information Form, End of Study Treatment Form, and Study Exit Form should be completed.

Study Treatment Recording

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

For **dosing interruptions**, where applicable, the following guidelines should be used:

- Related to AE:
    - On the Dose Administration Forms(s), dose change/missed should be indicated with AE as the reason. The dosing stop date must correlate to the AE/SAE start/stop dates.
- Related to Logistics:
    - For subjects who have missed a study treatment due to an inability to travel to the clinic or for some other logistical reason, on the Dose Administration Form(s) dose change/missed should be indicated with Other as the reason, and "Logistic" as Other, Specify.

If these options are not available in the eCRF, then either dose discontinuation should be recorded (if permanently stopped) or a protocol deviation should be recorded, prefixed COVID19.

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

Capturing Telephone Contacts with Subjects

If a telephone visit is substituted for an onsite study visit, the following are guidelines for data capture:

1. If the visit is specified as a phone visit as per protocol, no additional action is required.
2. If the visit is listed as on-site but the subject will be contacted by phone, data should be completed as per a normal visit (i.e., using the relevant eCRF pages to capture a phone Visit Date), and any possible assessment that can be obtained remotely should be captured, such as AEs, study drug administration and/or concomitant medications, and any additional safety information. All assessments that cannot be performed should be marked as not done or eCRF inactivated/marked Blank. A protocol deviation should be recorded in the clinic notes prefixed COVID19 detailing the use of a phone visit in place of an onsite

visit.

3. If the visit requires procedures that cannot be performed via telephone contact (e.g., MRI or CT scan), this should be discussed with the site monitor because this procedure may impact primary efficacy or safety analyses.

ACALABRUTINIB SITE-TO-SUBJECT DRUG SHIPMENT INSTRUCTIONS DURING PANDEMIC CONTAINMENT OR IN CASE OF FORCE MAJEURE

If a subject is definitively unable to physically go to the study site or unable to be represented by a third person because of pandemic containment or other force majeure, the study site's pharmacy may ship the study drug to the home of the subject following approval by the Sponsor.

For such a shipment, the following conditions must be met:

- The Sponsor is responsible for delivery of the study drug to the study site. Any shipments made from the site to the subject will be the responsibility of the study site.
- The subject is informed about the shipment method, confirms the address for receipt of the drug, and agrees that his or her personal information (i.e., name and address) may be given to a professional carrier.
- The pharmacy securely packages the drug for shipment.
- A professional carrier is used by the pharmacy to ship the drug securely and maintain chain of custody, with evidence provided. Acalabrutinib must be stored and shipped at room temperature (15°C to 30°C). The professional carrier must ensure that temperature monitoring is conducted for all shipments.
- To respect patient confidentiality, the carrier should only be given the name and address of the subject. The Sponsor should not receive any personal information about the subject.
- A procedure is defined with the carrier to confirm the receipt of the drug by the subject and that it is received in good condition.
- The site contacts the subject to confirm the receipt and integrity of the drug and gives instructions about the drug administration.
- The pharmacy completes its accountability with each shipment made directly to a subject.

Appendix 9. Medication Error, Drug Abuse, and Drug Misuse

Medication Error

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

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

Medication error includes situations where an error:

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

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

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

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

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

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

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic

intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

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

Examples of drug abuse include but are not limited to:

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

Drug Misuse

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

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

Examples of drug misuse include but are not limited to:

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

Appendix 10. Data Quality Assurance

All subject data relating to the study will be recorded on eCRF unless transmitted to AstraZeneca or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

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

At the final data cut-off, the clinical database will be closed to new data collection, however SAEs must continue to be reported via paper form.

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

Monitoring details describing strategy, methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are included in the Monitoring Plan.

AstraZeneca assumes accountability for actions delegated to other individuals (eg, CROs).

Record retention must align with GRAD (code 0102 Investigator Site File). In some markets the local requirement is less than 25 years e.g. Canada 15 years. If you are running a study in these countries please align to the local requirement and apply the appropriate GRAD exception.

Appendix 11. Dissemination of Clinical Study Data

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

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

Appendix 12. Country Specific Requirements

Canada specific Amendments

Version 6.1 - 22 February 2021

This amendment was considered non-substantial as the rational for all changes were for clarification. Clarifying edits and typographical changes were made throughout the protocol. The following substantive changes were made as part of this amendment:

Sections Impacted	Rationale
Synopsis, Section 3.1, Appendix 6 Clarified that subjects in Canada are not required to participate in the lenalidomide REMS program	For country-specific reasons, this requirement does not and will not apply to subjects in Canada
Section 4.0 Added sentence to reference new appendix for management of study procedures during pandemic.	Reference to new appendix was added.
Section 6.3.4, Section 6.3.5, and Section 7.1.2 Updates were made to the designee for receipt of serious adverse events and pregnancy reporting from Acerta Pharma Drug Safety to AstraZeneca Representative	Updated contact information
Appendix 5, Added ± 2 day window for Cycle 1 Day 1	Defined the time window for capturing the blood sample and pregnancy test within 48 hours prior to C1D1.
Appendix 6 Added ± 2 day window for Day 1 Added column header for Cycle 2 to include ± 2 day window	For logisitic reasons, challenge for dosing on same day as the visit assessments are performed.
Appendix 7 Management of Study Procedures During Pandemic	Added appendix to consolidate guidance for subject safety and ongoing access to medical care and investigational product during the global COVID-19 pandemic.

Version 7.0 - 14 July 2022

This protocol was amended to update the safety language from the most recent acalabrutinib Investigator's Brochure (version 11), to implement commercial drug transition language, and update the end of study definition.

Clarifying edits and typographical changes were made throughout the protocol. The following substantive changes were made as part of this amendment:

Sections Impacted	Rationale	Substantial / Non-substantial
Study Synopsis; Section 3.1 DESCRIPTION OF STUDY; Section 3.4.1 Inclusion Criteria Part 1; Section 3.4.3 Inclusion Criteria Part 2; Section 3.4.5 Inclusion Criteria Part 3; Section 3.7.2 Risks Associated with Rituximab (Rituxan/MabThera) Treatment; Section 3.7.6 Reproductive Toxicity; Section 6.2.3 Adverse Events of Special Interest	To align with the current local labels for lenalidomide and rituximab	Non-substantial

Updated contraceptive recommendations for lenalidomide and rituximab, rituximab contraindications, and rituximab warnings and precautions to align with the current local label recommendations. In addition, added suspected transmission of an infectious agent as an adverse event of special interest due to the use of rituximab in this study.		
Study Synopsis; Section 3.1 DESCRIPTION OF STUDY; Section 3.2 END OF STUDY; Section 4.3 SAFETY FOLLOW-UP VISIT; Section 6.3 DOCUMENTING AND REPORTING OF ADVERSE AND SERIOUS ADVERSE EVENTS; Section 6.3.5 Expedited Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest; Appendix 4. Schedule of Assessments Part 1; Appendix 5. Schedule of Assessments Part 2; Appendix 6. Schedule of Assessments Part 3 Clarified timings of final data cut-offs, end of study definition and added text to describe the continued treatment and monitoring of subjects still on acalabrutinib at the time of final data cut-off who are deriving clinical benefit from acalabrutinib treatment.	To provide clarification on continued treatment at the time or final data cut-off.	Non-substantial
Study Synopsis; Section 3.6.3 Cautionary Therapy Considerations Including Drug-Drug Interactions Added guidance for when acalabrutinib is used with a strong or moderate CYP3A inhibitor.	To align with guidance in local labels (such as the US Prescribing Information) on acalabrutinib dose adjustment when given with a strong or moderate CYP3A inhibitor.	Substantial
Section 3.7.1 Risks Associated with Acalabrutinib Treatment Text updated to advise that institutional guidelines should be followed in the management of infections, and atrial fibrillation. Previous PML and Hepatitis B Reactivation text removed as incorporated under the important identified risk of Infections. In addition, a new section for “Contraindications” added, for which there are none for acalabrutinib, and a new section for “Important Potential Risks” added with an overview on hepatotoxicity events.	To align with the acalabrutinib Investigator’s Brochure version 10 and version 11.	Substantial
Section 4.1.7 Physical Examination, Vital Signs,	To align with	Non-substantial

Height, and Weight Text updated to note nervous system examination will include attention to neurologic signs and symptoms of PML.	project-specific standards.	
Section 6.3.1 Adverse Event Reporting Period Text revised for clarity.	To align with project-specific adverse event collection standards.	Non-substantial
Throughout Minor editorial, formatting, and typographical updates and corrections have been made.	Minor corrections made for document clarity	Non-substantial

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Document Name: ace-ly-003-csp-v8		
Document Title:	ACE-LY-003 Clinical Study Protocol version 8	
Document ID:	Doc ID-005273683	
Version Label:	1.0 CURRENT LATEST APPROVED	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
13-Oct-2023 11:59 UTC	PPD	Management Approval
13-Oct-2023 12:06 UTC	PPD	Management Approval
19-Oct-2023 17:50 UTC	PPD	Content Approval
13-Oct-2023 17:42 UTC	PPD	Content Approval

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