


**A Phase 1/2, Multicenter, Open-label, and Dose-escalation Study
of ACP-196 in Subjects with Chronic Lymphocytic Leukemia, Richter's Syndrome
or Prolymphocytic Leukemia**


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Drug Product: ACP-196 (acalabrutinib)

Medical Monitor: PPD


Sponsor: Acerta Pharma BV (A Member of the AstraZeneca Group)
PPD

The Netherlands

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Amendment 13 Date: Version 13.0 – 25 August 2021

Confidentiality Statement

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INVESTIGATOR'S AGREEMENT: AMENDMENT 13

I have carefully read Protocol ACE-CL-001 entitled "A Phase 1/2, Multicenter, Open-label, and Dose-escalation Study of ACP-196 in Subjects with Chronic Lymphocytic Leukemia, Richter's Syndrome or Prolymphocytic Leukemia"

I agree to conduct this study as outlined herein and in compliance with Good Clinical Practices (GCP), all applicable regulatory requirements, and with the ethical principles laid down in the Declaration of Helsinki. Furthermore, I understand that the Sponsor, Acerta Pharma, 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 Acerta Pharma. All data pertaining to this study will be provided to Acerta Pharma. The policy of Acerta Pharma requires that any presentation or publication of study data by clinical investigators be reviewed by Acerta Pharma, before release, as specified in the protocol.

Signature

Print Name of Principal investigator

Date (DD Month YYYY)

SUMMARY OF AMENDMENT 13

This protocol is being amended to describe the continued treatment after data cutoff with acalabrutinib when commercially available or not commercially available in a particular country.

The substantive changes that were made as part of this amendment are as follows:

Change	Rationale
Section 3.1.3 End of Study Added language regarding continued treatment with acalabrutinib after data cutoff (associated with final database lock) whether acalabrutinib is commercially available or not.	To implement commercial drug transition language.

PROTOCOL SYNOPSIS

Protocol Number:	ACE-CL-001
Study Drug:	ACP-196 (acalabrutinib)
Protocol Title:	A Phase 1/2, Multicenter, Open-label, and Dose-escalation Study of ACP-196 in Subjects with Chronic Lymphocytic Leukemia, Richter's Syndrome or Prolymphocytic leukemia
Phase:	Phase 1/2
Study period:	Approximately 7 years, until final data cutoff (DCO); approximately >5 years, until last subject last visit (LSLV) (total of >12 years)
Comparator:	None
Background and Rationale for Study	<p>Clinical studies have shown that targeting the B-cell receptor (BCR) signaling pathway by inhibiting Bruton tyrosine kinase (BTK) produces significant clinical benefit in patients with non-Hodgkin lymphoma (NHL).</p> <p>Acerta Pharma BV (Acerta Pharma) has developed a potent, highly selective, orally bioavailable BTK inhibitor, acalabrutinib (also known as ACP-196 and Calquence®).</p> <p>The purpose of this study is to evaluate the safety and efficacy of acalabrutinib in the treatment of subjects with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), Richter's syndrome, or prolymphocytic leukemia transformation.</p>
Study Design:	<p>This study is a multicenter (approximately 15 global centers), open-label, nonrandomized, sequential group, dose-escalation study. In the Phase 1 portion of the study, the following dose cohorts will be evaluated:</p> <p>CCI [REDACTED] Dosing Cohorts</p> <p>Cohort 1: CCI [REDACTED]</p> <p>Cohort 2a: CCI [REDACTED]</p> <p>Cohort 3: CCI [REDACTED]</p> <p>Cohort 4a: CCI [REDACTED]</p> <p>CCI [REDACTED] Dosing Cohorts</p> <p>Cohort 2b: CCI [REDACTED]</p> <p>Cohort 4b: CCI [REDACTED]</p> <p>Dose-limiting toxicity (DLT) reviews have occurred for all cohorts and no DLTs were observed. Consequently, no maximum tolerated dose (MTD) has been reached. The Phase 2 portion of</p>

the study expands Cohort 2b to approximately 65 subjects and adds Cohort 2c at a dosage of CCI [REDACTED] for up to 30 subjects. Both cohorts are for subjects with relapsed or refractory CLL.

The Phase 2 portion of this study also includes 4 treatment subgroups to evaluate additional subpopulations with up to 30 subjects per cohort (except for Cohorts 10 and 11, which will have up to 6 and 60 subjects, respectively):

- Treatment Naive Group:
 - Cohort 7: CCI [REDACTED] (N = 11 to 30)
 - Cohort 11: CCI [REDACTED] (N = 11 to 60)
- Ibrutinib Intolerant Group: Cohort 8: CCI [REDACTED] (N = 11 to 35)
- Richter's Syndrome/ Prolymphocytic leukemia Transformation Group: Cohort 9: CCI [REDACTED] (N = 11 to 30)
- Ibrutinib R/R Group: Cohort 10: CCI [REDACTED] (N = 6)

Note: Under Amendment 6 of this protocol, all subjects will be switched to CCI [REDACTED] except for subjects in the Richter's Syndrome/Prolymphocytic Leukemia and Ibrutinib R/R groups (Cohort 9 and Cohort 10, respectively). Subjects in Cohort 4b will be switched from CCI [REDACTED]. Any subjects not switched to CCI [REDACTED] will need to be reviewed with the medical monitor.

Treatment with acalabrutinib may be continued for CCI [REDACTED] until disease progression or an unacceptable drug-related toxicity occurs. Subjects who meet criteria of disease progression and are continuing to gain clinical benefit from therapy may be able to temporarily remain on acalabrutinib after discussion with the medical monitor. All subjects who discontinue study drug will have a safety follow-up visit 30 (+ 7) days after the last dose of study drug, regardless of whether the subject receives a new anticancer therapy or demonstrates disease progression within this timeframe.

For all cohorts except Cohort 9, radiologic tumor assessment will be done at screening and at the end of Cycle 2, Cycle 4, and Cycle 6, then every 6 cycles until Cycle 36, and then every 12 cycles thereafter. For subjects in Cohort 9, radiologic tumor assessment will be done at screening and at the end of Cycle 2, Cycle 4, Cycle 6, Cycle 9, Cycle 12, Cycle 15, Cycle 18, Cycle 21, Cycle 24, and every 6 cycles thereafter. Otherwise, radiologic tumor assessments are done at investigator discretion.

Confirmation of complete response (CR) will require bone marrow analysis and radiologic tumor assessment (as applicable for subjects in Cohort 9). For subjects who remain on study for > 11 months, a mandatory bone marrow aspirate and biopsy is

	<p>required in Cycle 12 concurrent with the radiologic tumor assessment.</p> <p>Note: Under amendment 9 of this protocol, subjects in all cohorts will synchronize their clinic visits and laboratory assessments (excluding the HBV testing that will be every 3 cycles regardless of the imaging/clinic frequency) with the new imaging scheduled visits.</p> <p>All subjects will have standard hematology, chemistry, and urinalysis safety panels done at screening. This study also includes pancreatic function assessment (serum amylase and serum lipase) through Cycle 6 due to the pancreatic findings in the 28-day Good Laboratory Practice (GLP) rat toxicity study. This study also includes cardiac troponin testing through Cycle 6 and echocardiograms at screening and at end of Cycle 6. Once dosing commences, all subjects will be evaluated for safety once weekly for the first 4 weeks, every other week for Cycle 2, and monthly thereafter. Blood samples will be collected in Cycle 1 for pharmacokinetics (PK)/^{CCI} assessments. Electrocardiograms (ECGs) will be done at screening, and on Day 1-2, 8, 15, 22, 28 of Cycle 1, Day 15 and 28 of Cycle 2, and monthly thereafter through Cycle 6 for a subset of subjects in the dose escalation cohorts (i.e., Cohorts 1, 2a, 2b, 3, 4a, and 4b). ECGs are done in triplicate for screening only. Thereafter, single ECGs are done unless a repeat ECG is required. Note: The Phase 1 portion of the study has been closed, therefore the intensive ECG schedule for the subjects in the dose-escalation cohorts has been completed.</p> <p>A study schema is provided at the end of this synopsis.</p>
Definition of Dose-limiting Toxicity	<p>The DLT review portion of the study is now over. However, during dose escalation a DLT was defined as any of the following events unless the adverse event (AE) is clearly related to disease progression or the subject's current medical history and associated comorbidities:</p> <ol style="list-style-type: none">1. Any Grade 3 or greater nonhematologic toxicity with the exception of alopecia and Grade 3 nausea, vomiting and diarrhea that respond to supportive therapy.2. The following hematologic toxicities should be considered as DLTs:<ol style="list-style-type: none">a. Grade 4 neutropenia lasting more than 5 days.b. Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia with bleeding, or any requirement for platelets transfusion.c. Grade 3 or greater febrile neutropenia (temperature ≥ 38.5 °C).d. Grade 4 anemia, unexplained by underlying disease.

	3. Dosing delay due to toxicity for > 7 consecutive days
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Study Objectives:	<p>Primary Objectives:</p> <ul style="list-style-type: none">• Establish the safety and the MTD of orally administered acalabrutinib in subjects with CLL/SLL• Determine the PK of orally administered acalabrutinib and identification of its major metabolite <p>Secondary Objective:</p> <ul style="list-style-type: none">• Evaluate tumor response by overall response rate (ORR), duration of response (DOR), and progression-free survival (PFS) <p>Exploratory Objective:</p> <ul style="list-style-type: none">• CCI [REDACTED]
Efficacy Parameters:	<ul style="list-style-type: none">• ORR by investigator assessment• DOR by investigator assessment• PFS by investigator assessment
Safety Parameters:	<ul style="list-style-type: none">• DLTs and MTD• Frequency, severity, and attribution of AEs based on the Common Terminology Criteria for Adverse Events (CTCAE v4.03 or higher) for hematologic and nonhematologic AEs
Pharmacokinetic Parameters:	<p>The plasma PK of acalabrutinib and a metabolite will be characterized using noncompartmental analysis. The following PK parameters will be calculated, whenever possible, from plasma concentrations of acalabrutinib:</p> <ul style="list-style-type: none">• AUC_{0-last}: Area under the plasma concentration-time curve calculated using linear trapezoidal summation from time 0 to time last, where "last" is the time of the last measurable concentration.• AUC_{0-12}: Area under the plasma concentration-time curve from 0 to 12 hours, calculated using linear trapezoidal summation.• AUC_{0-24}: Area under the plasma concentration-time curve from 0 to 24 hours, calculated using linear trapezoidal summation.• AUC_{0-inf}: Area under the plasma concentration-time curve from 0 to infinity, calculated using the formula: $AUC_{0-inf} = AUC_{0-last} + C_{last} / \lambda_z$, where λ_z is the apparent terminal elimination rate constant.

	<ul style="list-style-type: none"> • $AUC_{0-24calc}$: Area under the concentration-time curve, from time 0 to 24 hour timepoint, 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) • $t_{1/2}$: Terminal elimination half-life (whenever possible) • λ_z: Terminal elimination rate constant (whenever possible) • CL/F: Oral clearance • V_z/F: Oral volume of distribution
CCI	
Sample Size:	Approximately 286 subjects
Inclusion Criteria:	<ol style="list-style-type: none"> 1. Men and women ≥ 18 years of age with a confirmed diagnosis of CLL/SLL, which has relapsed after, or been refractory to, ≥ 2 previous treatments for CLL/SLL. 2. Must have measurable CLL/SLL defined as ≥ 1 lymph node ≥ 2 cm as measured in the longest diameter. 3. Active disease meeting ≥ 1 of the following IWCLL 2008 criteria for requiring treatment: <ol style="list-style-type: none"> a. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia (hemoglobin < 10 g/dL) and/or thrombocytopenia (platelets $< 100,000/\mu\text{L}$). b. Massive (i.e., ≥ 6 cm below the left costal margin), progressive, or symptomatic splenomegaly. c. Massive nodes (i.e., ≥ 10 cm in the longest diameter), progressive, or symptomatic lymphadenopathy. d. Progressive lymphocytosis with an increase of $> 50\%$ over a 2-month period or a lymphocyte doubling time (LDT) of < 6 months. LDT may be obtained by linear regression extrapolation of absolute lymphocyte counts (ALC) obtained at intervals of 2 weeks over an observation period of 2 to 3 months. In subjects with initial blood lymphocyte counts of $< 30 \times 10^9/\text{L}$ ($30,000/\mu\text{L}$), LDT should not be used as a single parameter to define indication for treatment. In addition, factors contributing to lymphocytosis or lymphadenopathy

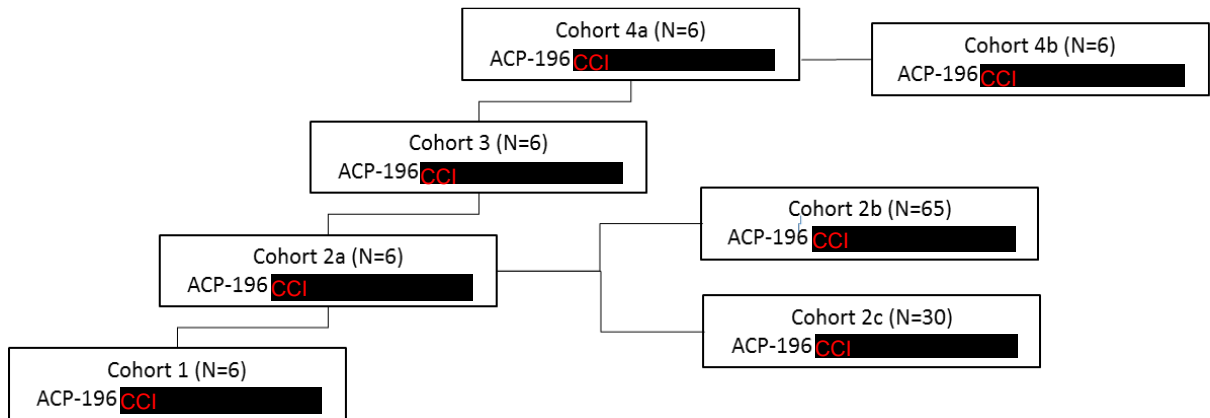
	<p>other than CLL (e.g., infections) should be excluded.</p> <ul style="list-style-type: none"> e. Autoimmune anemia and/or thrombocytopenia that is poorly responsive to standard therapy. f. Constitutional symptoms documented in the subject's chart with supportive objective measures, as appropriate, defined as ≥ 1 of the following disease-related symptoms or signs: <ul style="list-style-type: none"> i. Unintentional weight loss $\geq 10\%$ within the previous 6 months before Screening. ii. Fevers higher than 100.5°F or 38.0°C for 2 or more weeks before Screening without evidence of infection. iii. Night sweats for > 1 month before Screening without evidence of infection. <p>4. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2.</p> <p>5. Agreement to use highly effective methods of contraception during the study and for 2 days after the last dose of study drug if sexually active and able to bear or beget children (see Section 3.7.9 for list of highly effective methods of contraception).</p> <p>6. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty.</p> <p>7. 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 subject privacy regulations).</p> <p>8. <i>Removed at Amendment 11.</i></p>
<p>Inclusion Criteria for Treatment Subgroups</p>	<ul style="list-style-type: none"> 1. Treatment Naive only: Men and women ≥ 18 years of age with confirmed diagnosis of CLL/SLL, who require treatment per National Cancer Institute (NCI) or International Working Group guidelines and a) do not want to receive chemoimmunotherapy or b) have comorbidities that would preclude chemoimmunotherapy. 2. Ibrutinib Intolerant only: Men and women ≥ 18 years of age with confirmed diagnosis of CLL/SLL who are not tolerating ibrutinib due to ibrutinib-related AEs. 3. Richter's Syndrome/Prolymphocytic Leukemia Transformation only: Men and women ≥ 18 years of age and biopsy proven diffuse large B cell lymphoma (DLBCL) Richter's transformation or prolymphocytic leukemia transformation.

	<p>4. Ibrutinib R/R only: Men and women ≥ 18 years of age with confirmed diagnosis of CLL/SLL whose best response after 2 cycles of ibrutinib therapy was SD or nonresponse or who initially responded to ibrutinib therapy and now have signs of clinical progression.</p>
<p>Exclusion Criteria:</p>	<ol style="list-style-type: none"> 1. Prior malignancy, except for adequately treated basal cell, squamous cell skin cancer or in situ cervical cancer. Subjects with other prior malignancies from which the subject has been disease free for ≥ 2 years may be included if approved by the medical monitor. 2. 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. 3. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or left ventricular ejection fraction (LVEF) $\leq 40\%$. 4. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease, partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass. 5. Any immunotherapy within 4 weeks of first dose of study drug. 6. For subjects with recent chemotherapy or experimental therapy the first dose of study drug must occur after 5 times the half-life of the agent(s). 7. Relapsed after, or refractory to, prior BTK inhibitor therapy (Note: Does not apply to Ibrutinib R/R or Richter's Syndrome Group). 8. Any history of Richter's transformation (Note: Does not apply to Richter's Syndrome Group). 10. Central nervous system (CNS) involvement by lymphoma. 11. Grade ≥ 2 toxicity (other than alopecia) continuing from prior anticancer therapy including radiation. 12. Known history of human immunodeficiency virus (HIV) or serologic status indicating active hepatitis C virus (HCV) or hepatitis B virus (HBV) infection or any uncontrolled active systemic infection. Subjects with hepatitis B core antibody positive who are surface antigen negative or who are hepatitis C antibody positive will need to have a negative

	<p>polymerase chain reaction (PCR) result before enrollment. Those who are hepatitis B surface antigen positive or hepatitis B PCR positive and those who are hepatitis C PCR positive will be excluded.</p> <ol style="list-style-type: none"> 13. Uncontrolled AIHA or ITP defined as declining hemoglobin or platelet count secondary to autoimmune destruction within the screening period or requirement for high doses of steroids (> 20 mg daily of prednisone daily or equivalent). 14. History of stroke or intracranial hemorrhage within 6 months prior to the first dose of study drug. 15. Requires treatment with proton-pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). 16. Requires anticoagulation with warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon) within 7 days of first dose of study drug. 17. Major surgery within 4 weeks before first dose of study drug. 18. ANC < 0.75 x 10⁹/L or platelet count < 50 x 10⁹/L unless there is bone marrow involvement. 19. Total bilirubin > 1.5 x ULN (total bilirubin ≤ 2.5 x ULN allowed in subjects with autoimmune hemolytic anemia that is otherwise controlled); and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3.0 x ULN unless disease related. 20. Serum amylase > 1.5 x ULN or serum lipase > 1.5 x ULN. 21. Significant screening ECG abnormalities including, 2nd degree AV block type II, 3rd degree block, Grade 2 or higher bradycardia, or QTc ≥ 480 ms. 22. Cardiac troponin I levels above the limit of normal as specified by the manufacturer. 23. Breast feeding or pregnant. 24. History of bleeding diathesis (e.g., hemophilia, von Willebrand disease). 25. Concurrent participation in another therapeutic clinical trial. 26. Estimated creatinine clearance of < 30 mL/min, calculated using the formula of Cockcroft and Gault [(140-Age) • Mass (kg)/(72 • creatinine mg/dL); multiply by 0.85 if female]. 27. Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before screening.
<p>Dosage Form:</p>	<p>Acalabrutinib is provided as hard gelatin capsules prepared using standard pharmaceutical grade excipients.</p>

Dose Regimen/Route of Administration:	Acalabrutinib is an orally administered product.
Statistics:	<p>No formal statistical tests of hypotheses will be performed. Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions for discrete variables) will be used to summarize data as appropriate.</p> <p>The Phase 1 trial design (dose-escalation) is specified because of its practical simplicity, use of a biomarker, and not because of power considerations. The MTD is defined as the largest daily dose for which fewer than 33% of the subjects experience a DLT during Cycle 1 during the dose-escalation phase of the protocol. The MTD was not reached on this protocol.</p> <p>The Phase 2 (expansion portion) of the study will test the null hypothesis that the ORR is $\leq 10\%$ against the alternative hypothesis that it is $\geq 35\%$. Using Simon's optimal 2-stage design (Simon 1989), a total sample size of 30 subjects per cohort has power = 0.90 to achieve a 1-sided significance level of ≤ 0.025. In Stage 1, 11 subjects will be enrolled per cohort; if ≥ 2 subjects (18%) achieve an objective response of a PR/PRL or better within the first 4 cycles of treatment, then that cohort will continue to full enrollment (Stage 2). Under the Simon design, an ORR of $\geq 23\%$ (i.e., ≥ 7 subjects responding of 30 subjects evaluated) will achieve a significance level of ≤ 0.025. Using an exact binomial confidence interval (CI), an ORR of 23% (i.e., 7 subjects responding of 30 subjects evaluated) will achieve a 2-sided 90% lower bound of 11.5%.</p>

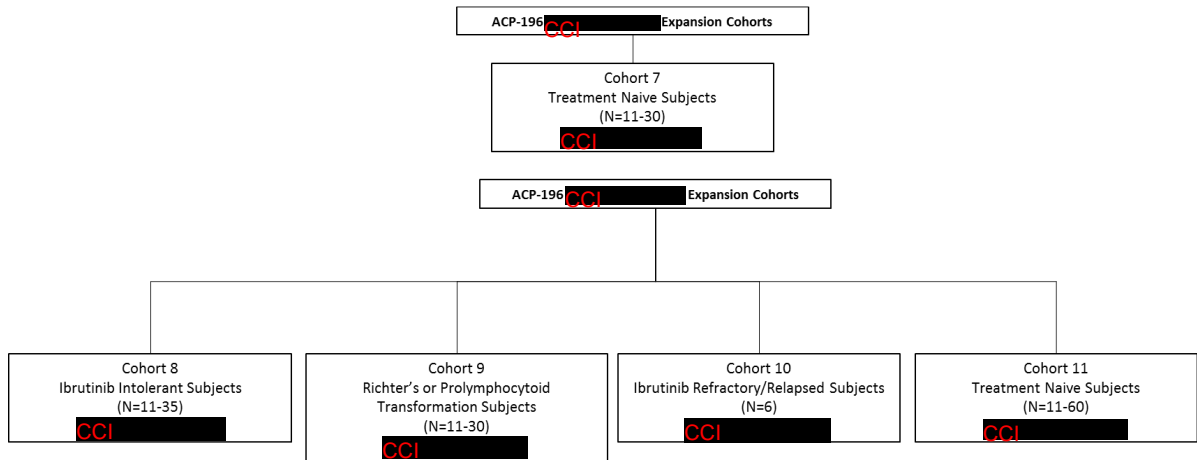
STUDY SCHEMA FOR DOSE-ESCALATION COHORTS



Note: No DLTs occurred during dose escalation and the MTD was not reached. Under Amendment 5 of the protocol, subjects in Cohort 1, Cohort 2a, and Cohort 4a will be switched to [redacted]. Under Amendment 6 of the protocol, subjects in Cohort 2c and in Cohort 4b [redacted] will be switched to [redacted].

Abbreviations: BID = twice daily; DLT = dose-limiting toxicity; MTD = maximum tolerated dose; QD = once daily

STUDY SCHEMA FOR TREATMENT SUBGROUPS



Note: Under Amendment 6 of the protocol, subjects in Cohort 7 will be switched to [REDACTED]
Abbreviations: BID = twice daily; QD = once daily

LIST OF ABBREVIATIONS

Abbreviation	Definition
λ_z	terminal elimination rate constant
ACP-196	Acalabrutinib
ADCC	antibody-dependent cell-mediated cytotoxicity
AE(s)	adverse event(s)
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HBc	hepatitis B core antibody
AST	aspartate aminotransferase
AUC	area under the curve
BCR	B-cell receptor
BCRP	breast cancer-related protein
BID	twice daily
BTK	Bruton tyrosine kinase
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practices
CL/F	oral clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CR	complete remission (response)
CRi	CR with incomplete blood count recovery
CSSF	Clinical Supplies Shipping Receipt Form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DCO	data cutoff
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
ECG	Electrocardiogram

Abbreviation	Definition
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
FcR	Fc receptor
FDA	Food and Drug Administration
FDG	[¹⁸ F]fluorodeoxyglucose
FISH	fluorescence in situ hybridization
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
hERG	human ether-à-go-go-related gene
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
ICF	informed consent form
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IGHV	immunoglobulin heavy-chain variable
IRB	Institutional Review Board
IRC	Independent Review Committee
ITK	Interleukin-2-inducible tyrosine kinase
IVIG	intravenous immunoglobulin
LDH	lactate dehydrogenase
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
mos	Months
MRD	minimal residual disease
MTD	maximum tolerated dose
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma

Abbreviation	Definition
NK	natural killer (cells)
NOAEL	no observable adverse effect level
ORR	overall response rate
PBMCs	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PD	Pharmacodynamics
PE	physical examination
PET	positron-emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PK	Pharmacokinetics
PML	progressive multifocal leukoencephalopathy
PR	partial remission (response)
PRL	partial remission (response) with lymphocytosis
QD	once daily
QM	every month
QTc	corrected QT interval
R/R	relapsed/refractory
SAE(s)	serious adverse event(s)
SD	stable disease
SLL	small lymphocytic lymphoma
SPD	sum of the product of the diameters
$t_{1/2}$	half life
T_{max}	time to maximum plasma concentration
ULN	upper limit of normal
V _z /F	oral volume of distribution
WHO	World Health Organization
XLA	X-linked agammaglobulinemia

TABLE OF CONTENTS

INVESTIGATOR'S AGREEMENT: AMENDMENT 13.....	2
SUMMARY OF AMENDMENT 13	3
PROTOCOL SYNOPSIS	4
STUDY SCHEMA FOR DOSE-ESCALATION COHORTS	14
STUDY SCHEMA FOR TREATMENT SUBGROUPS	15
LIST OF ABBREVIATIONS	16
TABLE OF CONTENTS	19
LIST OF TABLES	23
LIST OF FIGURES	24
LIST OF APPENDICES	25
1. INTRODUCTION.....	26
1.1. Role of BTK in Lymphoid Cancers	26
1.2. Preclinical Studies.....	27
1.2.1. Chemistry.....	27
1.2.2. Mechanism of Action of Acalabrutinib.....	28
1.2.3. Dog Lymphoma Study.....	28
1.2.4. Acalabrutinib and Antibody-dependent Cell-mediated Cytotoxicity.....	28
1.2.5. Acalabrutinib and Thrombus Formation.....	29
1.2.6. Safety Pharmacology	30
1.2.7. Drug-drug Interaction Potential.....	31
1.2.8. General Toxicity Studies	32
1.3. Clinical Experience	32
1.3.1. Pharmacokinetics and Pharmacodynamics of Acalabrutinib in Healthy Volunteers	32
1.3.2. Clinical Experience of Acalabrutinib in CLL	34
1.4. Risks/Benefits	34
1.5. Summary and Conclusions	35
2. STUDY OBJECTIVES.....	35
2.1. Primary Objectives.....	35
2.2. Secondary Objective	35
2.3. Exploratory Objective	35
3. INVESTIGATIONAL PLAN	35
3.1. Overall Study Design	36
3.1.1. Escalation Portion – Phase 1	36
3.1.2. Expansion Cohorts – Phase 2	36
3.1.3. End of Study.....	39

3.2.	Study Parameters	40
3.2.1.	Efficacy Parameters	40
3.2.2.	Safety Parameters.....	40
3.2.3.	Pharmacokinetic and CCl Parameters	41
3.3.	Rationale for Study Design and Dosing Regimen.....	41
3.4.	Selection of Study Population	41
3.4.1.	Inclusion Criteria	41
3.4.2.	Inclusion Criteria for Treatment Subgroups	43
3.4.3.	Exclusion Criteria	43
3.4.4.	Replacement of Subjects.....	44
3.4.5.	Enrollment Procedures	45
3.5.	Study Drug: Acalabrutinib Hard Gelatin Capsule.....	45
3.5.1.	Premedications	45
3.5.2.	Formulation, Packaging, and Storage	45
3.5.3.	Administration of Acalabrutinib	46
3.5.4.	Assuring Subject Compliance.....	46
3.5.5.	Study Treatment Schedule	46
3.6.	Concomitant Therapy.....	47
3.6.1.	Permitted Concomitant Therapy	47
3.6.2.	Prohibited Concomitant Therapy	47
3.7.	Risks Associated with Acalabrutinib Treatment.....	47
3.7.1.	Hemorrhage	47
3.7.2.	Infections.....	48
3.7.3.	Cytopenias	49
3.7.4.	Second Primary Malignancies	49
3.7.5.	Atrial Fibrillation.....	49
3.7.6.	Reference Safety Information	49
3.7.7.	Dietary Restrictions	49
3.7.8.	Drug-drug Interactions.....	50
3.7.9.	Reproductive Toxicity	51
3.7.10.	Overdose Instructions	52
3.8.	Assessment of Dose Limiting Toxicity	53
3.9.	Assessment of QTc Interval Prolongation by Central ECG Testing	53
3.10.	Stopping Rules.....	54
3.11.	Dosing Delays and Modifications	55
3.12.	Data and Safety Monitoring.....	55
4.	STUDY ACTIVITIES AND ASSESSMENTS.....	55
4.1.	Description of Procedures	60
4.2.	Investigator’s Assessment of Response to Treatment.....	66

4.3.	Safety Follow-up Visit.....	70
4.4.	Missed Evaluations	70
5.	ASSESSMENT OF SAFETY	70
5.1.	Definitions	71
5.1.1.	Adverse Events	71
5.1.2.	Serious Adverse Event.....	72
5.1.3.	Severity.....	73
5.1.4.	Adverse Events of Special Interest.....	74
5.2.	Documenting and Reporting of Adverse and Serious Adverse Events	74
5.3.	Adverse Event Reporting Period	74
5.4.	Assessment of Adverse Events.....	74
5.5.	Second Primary Malignancies.....	75
5.6.	Pregnancy.....	76
5.7.	Expedited Reporting Requirements for Serious Adverse Events <i>and</i> Adverse Events of Special Interest	76
5.8.	Type and Duration of Follow-up of Subjects After Adverse Events.....	77
5.9.	Hy's Law	77
6.	STATISTICAL METHODS OF ANALYSIS.....	78
6.1.	General Considerations and Determination of Sample Size	78
6.2.	Definition of Analysis Populations	79
6.3.	Missing Data Handling	79
6.4.	Endpoint Data Analysis	79
6.4.1.	Safety Endpoint.....	79
6.4.2.	Demographics and Baseline Characteristics	80
6.4.3.	Analysis of Efficacy Parameters	80
6.4.4.	Analysis of Pharmacokinetic / CCI Parameters	80
7.	STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS	81
7.1.	Regulatory and Ethical Compliance	82
7.2.	Institutional Review Board and Independent Ethics Committee.....	82
7.3.	Informed Consent and Protected Subject Health Information Authorization.....	82
7.4.	Subject Screening Log	83
7.5.	Case Report Forms.....	83
7.6.	Study Monitoring Requirements	83
7.7.	Investigational Study Drug Accountability.....	84
7.8.	Record Retention	85

7.9. Protocol Amendments.....	86
7.10. Publication of Study Results.....	86
7.11. Clinical Trial Insurance.....	86
7.12. General Investigator Responsibilities	86
8. REFERENCES.....	88

LIST OF TABLES

Table 3-1. QTc Toxicity Grading Defined by CTCAE	54
Table 4-1. Schedule of Assessments.....	57
Table 4-2. ECG Acquisition Times.....	62
Table 4-3. Pharmacokinetic Sample Schedule	65
Table 4-4. Response Assessment Criteria for CLL/SLL (modified from Hallek 2008).....	67
Table 4-5. Response Assessment Criteria for Richter's Syndrome (Cheson 2014).....	69
Table 6-1. Two-Sided Exact 90% CIs for ORR in Expansion Cohorts (N = 30)	78

LIST OF FIGURES

Figure 1-1. NK Cell Natural Cytotoxicity.....29
Figure 1-2. In Vivo Thrombus Formation30

LIST OF APPENDICES

Appendix 1 Examples of Coadministered Drugs That Need Additional
Consideration.....90

Appendix 2 ECOG Performance Status.....92

Appendix 3 Adverse Event Assessment of Causality93

Appendix 4 Actions Required in Cases of Increases in Liver Biochemistry
and Evaluation of Hy’s Law94

Appendix 5 Management of Study Procedures During Pandemic.....99

1. INTRODUCTION

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 2009, Bradshaw 2010).

Functional null mutations of BTK in humans cause the inherited disease, X-linked agammaglobulinemia (XLA), which is characterized by a lack of mature peripheral B cells (Vihinen 2000). Conversely, BTK activation is implicated in the pathogenesis of several B-cell malignancies (Buggy 2012). Taken together, these findings have suggested that inhibition of BTK may offer an attractive strategy for treating B-cell neoplasms.

Ibrutinib (PCI-32765) (IMBRUVICA®), an oral, small-molecule BTK inhibitor has been developed clinically for the treatment for B-cell malignancies and received marketing approval in the United States in November 2013 and in the European Union in October 2014. The nonclinical and early clinical findings with ibrutinib have created the foundation on which agents, such as acalabrutinib (also known as ACP-196 and Calquence®), will be developed.

In Phase 1/2 clinical testing as a monotherapy in subjects with hematologic malignancies (Advani 2013, Byrd 2013, Wang 2013), ibrutinib was generally well tolerated at dose levels through 840 mg (the highest dose tested). No maximum tolerated dose (MTD) was apparent within the tested dose range. Furthermore, subjects typically found the drug tolerable over periods extending to > 2 years. No overt pattern of myelosuppression was associated with ibrutinib treatment. No drug-related reductions in circulating CD4⁺ cells or serum immunoglobulins were noted. Adverse events (AEs) with an apparent relationship to study drug included diarrhea, rash, severe hemorrhage and atrial fibrillation.

While highly potent in inhibiting BTK, ibrutinib has also shown in vitro activity against other kinases with a cysteine in the same position as Cys481 in BTK to which the drug covalently binds. The inhibition of epidermal growth factor receptor (EGFR) is also observed in cellular assays and may be the cause of ibrutinib-related AEs of diarrhea and rash (IMBRUVICA® prescribing information). In addition, ibrutinib is a substrate for CYP3A; inhibition of CYP3A causes a 29-fold increase in maximum concentration (C_{max}) and 24-fold increase in area under the curve (AUC) for ibrutinib (IMBRUVICA®).

prescribing information). This increases the possibility of drug-drug interactions in combination therapies with drugs currently used in management of subjects with cancer. These liabilities support the development of alternative BTK inhibitors for use in the therapy of B-cell malignancies.

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 encouraging activity and acceptable safety in nonclinical studies. Acalabrutinib is a potent, highly selective covalent inhibitor of BTK, which shows greater kinase selectivity for BTK than ibrutinib in laboratory studies. Key nonclinical differentiators of acalabrutinib versus ibrutinib are:

Acalabrutinib has been evaluated against ibrutinib in EGFR expressing cell lines. Ibrutinib is a potent covalent inhibitor of EGFR ($EC_{50} = 5.3$ nM). Acalabrutinib did not inhibit EGFR even at the highest concentration tested (10 μ M).

- Acalabrutinib and ibrutinib have been evaluated in natural killer (NK) cell functional assays. While ibrutinib inhibits NK cell functions including antibody-dependent cellular cytotoxicity (ADCC), lytic granule release and cytokine production (Kohrt 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 CLL patients treated with acalabrutinib had similar thrombus formation dynamics as platelets from healthy volunteers, while platelets from ibrutinib-treated CLL patients had impaired thrombus formation (Byrd 2016).

The nonclinical and toxicology results of acalabrutinib suggest 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. Preclinical Studies

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

1.2.1. Chemistry

CCI

Acalabrutinib is orally bioavailable in animals and human subjects, and is suitable for

formulating in capsules. For clinical testing, acalabrutinib has been manufactured and formulated according to current Good Manufacturing Practices (cGMP).

Calquence® has been approved in the United States and other markets for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy, chronic lymphocytic leukemia (CLL), and small lymphocytic lymphoma (SLL).

1.2.2. Mechanism of Action of Acalabrutinib

Acalabrutinib was specifically designed to be a more potent and selective inhibitor of BTK to avoid off-target side effects as seen with ibrutinib. When profiled against 395 human kinases, acalabrutinib is more selective than ibrutinib (Byrd 2016). For more detailed information please refer to the Investigator Brochure.

1.2.3. Dog Lymphoma Study

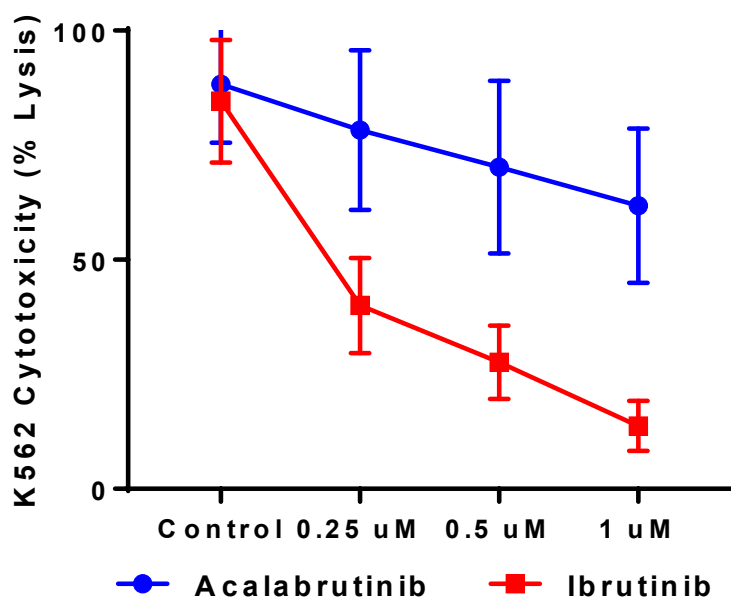
Spontaneous canine B-cell lymphoma shares many characteristics with human NHL, including diagnostic classifications and response to BTK inhibition (Honigberg 2010). The life expectancy in untreated animals with aggressive disease is ~6 weeks, thus enabling rapid assessment of drug efficacy (Vail 2004). Acalabrutinib was evaluated in a dose-escalation study in canine spontaneous B-cell lymphoma (Harrington 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 adverse events consisting primarily of grade 1 or 2 anorexia, weight loss, vomiting, diarrhea and lethargy. Per Veterinary Cooperative Oncology Group criteria for assessment of response in peripheral nodal lymphoma (Vail 2010), the overall response rate (ORR) was 25% (5/20) with a median progression free survival (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 non-Hodgkin lymphoma (NHL). These findings are similar to the clinical responses (i.e., 1 dog with PR out of 5 dogs treated with suspected or confirmed DLBCL) observed with ibrutinib in dogs with spontaneous B-cell lymphoma (Honigberg 2010).

1.2.4. Acalabrutinib and Antibody-dependent Cell-mediated Cytotoxicity

As acalabrutinib is not an inhibitor of inducible tyrosine kinase (ITK), it is expected to have less activity against non-malignant cells that require ITK for development and functional activation, such as T and NK cells. ITK kinase is required for FcR-stimulated NK cell function including calcium mobilization, granule release, and overall antibody-dependent cell-mediated cytotoxicity (ADCC). Anti-CD20 antibodies are

standard of care drugs, often as part of combination regimens, for the treatment of CD20⁺ B-cell malignancies; obinutuzumab has been specifically designed to increase Fc interactions and promote ADCC and phagocytosis of malignant CD20⁺ cells. Ibrutinib has been evaluated for effects on NK activity, including ADCC, using in vitro assays of cytokine release, lytic granule release, and cellular cytotoxicity (Kohrt 2014). In contrast to more specific BTK inhibitors, ibrutinib inhibited all these NK cell functions, and impaired NK activity against rituximab-coated autologous CLL cells and in mouse tumor models requiring Fc mediated effector functions (Kohrt 2014). Acalabrutinib was tested in ADCC and natural cytotoxicity assays, using cells from healthy donors. In these in vitro tests, NK cell function was preserved with acalabrutinib treatment, whereas ibrutinib inhibited functional activity, including natural cytotoxicity against K562 cells.

Figure 1-1. NK Cell Natural Cytotoxicity



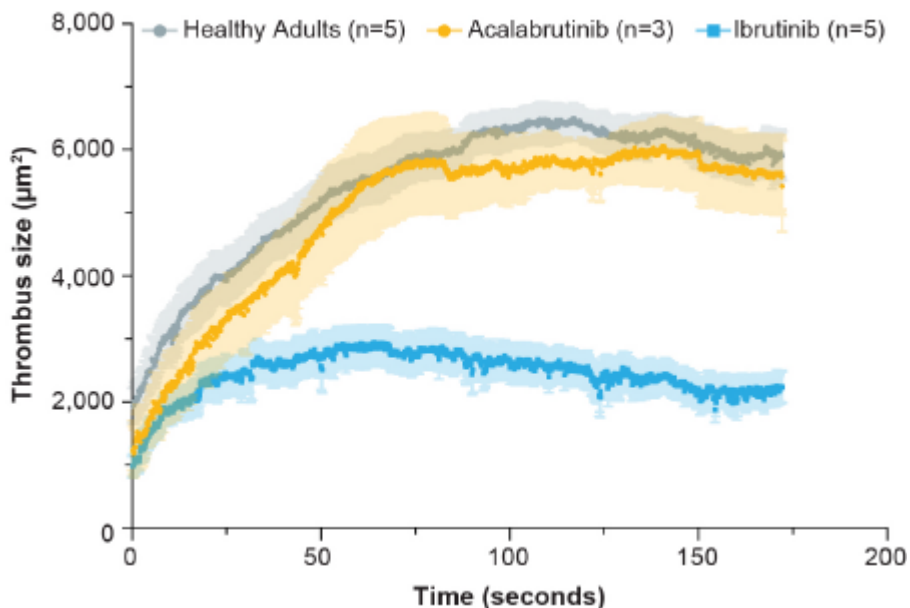
Peripheral blood mononuclear cells were cultured with ⁵¹Cr labelled K562 targets at an E:T ratio of 100:1 for 4 hours. Cytotoxicity was evaluated by scintillation counting of supernatants. Treatment, dose and interaction effect were significant in 2-way ANOVA (n=5 healthy donors; ibrutinib vs acalabrutinib p < 0.0001; all ibrutinib doses p < 0.0001 compared with control; p = 0.0117 for control vs acalabrutinib 1µM, other acalabrutinib doses not statistically different from control condition).

1.2.5. Acalabrutinib and Thrombus Formation

Ibrutinib is associated with an increased risk of bleeding (Kamel 2014). Hence, the effects of acalabrutinib and ibrutinib were evaluated on human platelet-mediated thrombus formation by using the in vivo human thrombus formation in VWF^{HA1} murine

model, which has been previously described (Chen 2008). The in vivo function of platelets isolated from blood of healthy volunteers (n=5), CLL subjects treated with 420 mg QD ibrutinib (n=5) or CLL subjects treated with 100 mg BID acalabrutinib (n=3) was evaluated in the VWF^{HA1} model. Results from this study showed a reduction in platelet-vessel wall interactions of platelets from ibrutinib-treated CLL subjects, but not of those from CLL subjects treated with acalabrutinib (Byrd 2016).

Figure 1-2. In Vivo Thrombus Formation



Platelets from subjects treated with ibrutinib 420 mg once per day (QD) (n=5) or acalabrutinib 100 mg twice per day (BID) (n=3) were evaluated for their ability to support thrombus formation in laser injured arterioles of VWFHA1 mice. Freshly isolated platelets from healthy volunteers (n=5) were used as non-drug treated controls. A minimum of 4 arterioles per mouse was used to assess thrombus formation for each patient/volunteer sample. Median fluorescence intensity as a function of time is provided in the figure (shading denotes standard error of the median).

1.2.6. Safety Pharmacology

In vitro and in vivo safety pharmacology studies with acalabrutinib have demonstrated a favorable nonclinical safety profile.

When screened at 10 µM in binding assays evaluating interactions with 80 known pharmacologic targets such as G-protein-coupled receptors, nuclear receptors, proteases, and ion channels, acalabrutinib shows significant activity only against the A3 adenosine receptor; follow-up dose-response experiments indicated a IC₅₀ of 1.5 µM, suggesting a low clinical risk of off-target effects. Acalabrutinib at 10 µM showed no inhibition of in vitro EGFR phosphorylation in an A431 human epidermoid cancer cell line whereas ibrutinib had an IC₅₀ of 66 nM.

The in vitro effect of acalabrutinib on human ether-à-go-go-related gene (hERG) channel activity was investigated in vitro in human embryonic kidney cells stably transfected with hERG. Acalabrutinib inhibited hERG channel activity by 25% at 10 µM, suggesting a low clinical risk that acalabrutinib would induce clinical QT prolongation as predicted by this assay.

Acalabrutinib was well tolerated in standard in vivo Good Laboratory Practices (GLP) studies of pharmacologic safety. A functional observation battery in rats at doses of through 300 mg/kg (the highest dose level) revealed no adverse effects on neurobehavioral effects or body temperature at any dose level. A study of respiratory function in rats also indicated no treatment-related adverse effects at doses through 300 mg/kg (the highest dose level). In a cardiovascular function study in awake telemeterized male beagle dogs, single doses of acalabrutinib at dose levels through 30 mg/kg (the highest dose level) induced no meaningful changes in body temperature, cardiovascular, or electrocardiographic (ECG) (including QT interval) parameters. The results suggest that acalabrutinib is unlikely to cause serious off-target effects or adverse effects on critical organ systems.

1.2.7. Drug-drug Interaction Potential

Based on available nonclinical and clinical data, acalabrutinib is metabolized by CYP3A, GSTM1/M2 and amide hydrolysis. CYP3A -mediated oxidation appears to be the major route of metabolism in humans. In a healthy volunteer study (ACE-HV-001), the effect of coadministration of a strong CYP3A and P-glycoprotein inhibitor, itraconazole, on the plasma levels of acalabrutinib was evaluated. The mean plasma acalabrutinib C_{max} and AUC_{0-inf} values increased 3.7- and 5.1-fold, respectively, in the presence of itraconazole relative to no pretreatment.

Based on results from study ACE-HV-112, consumption of grapefruit juice, which can result in CYP3A inhibition, will not result in substantially increased exposure to acalabrutinib. Therefore, restrictions on grapefruit juice or Seville orange consumption are not necessary.

In a healthy volunteer study (ACE-HV-004), rifampin, a strong CYP3A inducer, dosed at CC decreased AUC to 23% of values obtained with acalabrutinib dosed alone. PBPK modeling predicted the magnitude of changes due to a variety of moderate CYP3A inducers and inhibitors.

Results from studies in healthy subjects, ACE-HV-004 and ACE-HV-112, showed that drugs that reduce gastric acidity can lower acalabrutinib exposure.

Acalabrutinib is unlikely to be a perpetrator of a drug-drug interaction at the level of inhibition or induction of CYP isoforms.

Acalabrutinib co-administration may increase exposure to breast cancer-related protein (BCRP) substrates by inhibition of intestinal BCRP.

For more detailed information, please refer to the Investigator Brochure.

1.2.8. General Toxicity Studies

The systemic toxicity of acalabrutinib has been fully evaluated in repeat-dose sub-chronic studies in mice, rats and dogs, reproductive toxicity studies in rats and rabbits, and ongoing chronic studies in rats and dogs. The pivotal GLP studies were 28- and 91-day repeat dose studies in rats and dogs, each with recovery periods to assess the reversibility of observed changes. 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, in subsequent studies the 100 mg/kg/day dose level was determined to be a no observable adverse effect level (NOAEL). In rats, the target organs of toxicity were the kidney, liver and heart.

The NOAEL in the dog 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 MTD, were the kidney and liver. Heart findings were also observed in 2 dogs with 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 sub-chronic studies or in the rat chronic toxicity study. However, in 5 of 6 rats from the 4-week study that died early at 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

1.3.1. Pharmacokinetics and Pharmacodynamics of Acalabrutinib in Healthy Volunteers

ACE-HV-001 was a PK/pharmacodynamic (PD), dose-ranging, food-effect, and drug-drug interaction study evaluating CCI in healthy

volunteers. This study evaluated the PK/PD of acalabrutinib at various dose levels and regimens. The starting dose for acalabrutinib was [CCI]. This study has been completed and no adverse laboratory, vital signs, or ECG findings were observed [CCI]. Three adverse events (AEs) related to study drug were reported. Each AE was Grade 1 and resolved without treatment. The AEs were constipation [CCI], feeling cold [CCI], and somnolence [CCI].

In Part 1, PK properties of acalabrutinib were evaluated after oral administration of [CCI]. Of the 30 subjects evaluated, all had observed systemic concentrations of acalabrutinib. Acalabrutinib plasma time to maximum concentration (T_{max}) values were between 0.5 and 1.0 hour for all dose cohorts and were independent of dose level. The increase in mean C_{max} values was greater than dose proportional based on the increases of C_{max} from the first dose administered. When evaluating AUC_{0-12} , AUC_{0-24} or AUC_{0-inf} , the mean values increased in a dose-proportional manner based on the increases of the total dose administered. Mean half-life ($t_{1/2}$) values ranged from 0.97 to 2.1 hours, and appeared to decrease as the dose increased. The mean calculated oral clearance (CL/F: 165 to 219 L/h) and volume of distribution values (Vz/F: 233 to 612 L) appeared to be independent of the dose administered.

Acalabrutinib was not detected in the urine of subjects receiving the [CCI] doses of acalabrutinib. Acalabrutinib was detected in urine of other subjects (0.4% to 0.6% of dose) and amounts increased in a dose dependent manner.

In Part 2, the effect of food on the PK of acalabrutinib [CCI] after a single oral administration was evaluated in 6 men and 6 women. Median time to maximum plasma acalabrutinib (T_{max}) values were increased in the fed state (2.5 hours) relative to the fasted state (0.5 hour). The mean plasma acalabrutinib C_{max} fed values decreased to 27.3% of the C_{max} values observed in the fasted state. In contrast, the relative AUC exposure of acalabrutinib remained mostly unchanged in both states. This decrease in exposure is not clinically significant; therefore, acalabrutinib can be taken without regard to meals.

In Part 3, the effect of itraconazole on the PK of acalabrutinib [CCI] after a single oral administration was evaluated in 17 subjects. No difference in acalabrutinib T_{max} values was observed in the presence or absence of itraconazole.

Mean acalabrutinib exposures (as assessed by C_{max} , AUC_{0-last} , AUC_{0-24} , and AUC_{0-inf}) increased in the presence of itraconazole. The mean plasma acalabrutinib C_{max} values increased 3.7-fold in the presence of itraconazole. The mean plasma AUC_{0-last} , AUC_{0-24} , and AUC_{0-inf} values also increased between 4.9- to 5.1-fold in the presence of itraconazole. Mean CL/F and Vz/F values decreased in the presence of itraconazole (CL/F: 217 vs 44 L/h; Vz/F: 1190 vs 184 L). No differences in half-life values were observed (3.3 vs 2.5 hours).

The PD of acalabrutinib was evaluated using a BTK occupancy assay and correlated with a functional assay that determines the level of BTK inhibition by measuring expression of CD69 and CD86 on B cells. A dose-dependent increase in BTK occupancy and corresponding decrease in CD69 and CD86 expression was observed in this study. Full BTK occupancy ($\geq 90\%$) and complete CD86 and CD69 inhibition ($\geq 90\%$) occurred at the [REDACTED] cohorts 1 to 3 hours after administration. However, only the [REDACTED] maintained high BTK occupancy (91.5%) and high BCR functional inhibition (CD86: $86 \pm 3\%$ and CD69: $78 \pm 8\%$) at 24 hours. For subjects receiving a [REDACTED] of acalabrutinib [REDACTED] [REDACTED] full BTK target occupancy was observed [REDACTED] [REDACTED] cohort (BTK occupancy $97 \pm 4\%$).

For more detailed information, please refer to the Investigator Brochure.

1.3.2. Clinical Experience of Acalabrutinib in CLL

No new safety concerns were identified for acalabrutinib monotherapy based on safety data available to date. The safety data of acalabrutinib monotherapy are consistent among studies. For detailed information on the clinical experience for acalabrutinib, refer to the Investigator Brochure.

1.4. Risks/Benefits

Acalabrutinib is a potent, orally bioavailable small-molecule inhibitor of BTK. A PK/PD study has been completed with acalabrutinib in healthy volunteers (ACE-HV-001; [Section 1.3](#)). The safety results showed no safety risk was identified in healthy subjects receiving [REDACTED] of ACP 196 [REDACTED]. In the dose escalation portion of CLL study ACE-CL-001, no DLTs have been identified at dosages of [REDACTED]. [REDACTED] The response rate in the evaluable subjects for this study is currently an ORR of 94% with some subjects obtaining PRs after only 2 cycles of therapy. In summary, the preliminary data suggest that acalabrutinib is well tolerated and has robust

activity as a single agent in the treatment of subjects with relapsed or refractory CLL/SLL including those with 17p del. Based on these results, addition of expansion cohorts of various treatment subgroups is warranted to further evaluate the efficacy and safety of acalabrutinib. The Phase 2 portion of this study also increases the number of subjects with previously treated or untreated CLL at the planned Phase 3 dosage of [REDACTED]

1.5. Summary and Conclusions

This study comprises evaluation of the safety and activity of a potent, highly selective, BTK inhibitor, acalabrutinib, in subjects with previously treated or untreated CLL/SLL or Richter's syndrome. The design and conduct of this study is supported by an understanding of the natural history and current therapies for subjects with CLL/SLL; knowledge of the activity and safety of the first-generation BCR inhibitor (i.e., ibrutinib) in subjects with B-cell malignancies; and the available nonclinical and clinical information regarding acalabrutinib. Clinical studies have shown that acalabrutinib is an orally bioavailable BTK inhibitor with fast absorption and rapid clearance that maintains optimal target coverage over 24 hours with a dosage of [REDACTED]. Acalabrutinib has been well tolerated in healthy volunteers and subjects with CLL or Richter's syndrome. Despite poor prognostic characteristics in the CLL study population, acalabrutinib has induced sustained decreases in lymphadenopathy and provides more rapid reduction and/or resolution of lymphocytosis than ibrutinib. No specific drug-related toxicity has been identified to date for acalabrutinib.

2. STUDY OBJECTIVES

2.1. Primary Objectives

- Establish the safety and the MTD of orally administered acalabrutinib in subjects with CLL/SLL.
- Determine pharmacokinetics (PK) of orally administered acalabrutinib and identification of its major metabolite

2.2. Secondary Objective

- Evaluate tumor response by ORR, DOR, and PFS

2.3. Exploratory Objective

- [REDACTED]

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

3.1.1. Escalation Portion – Phase 1

This study is a multicenter (approximately 15 global centers), open-label, nonrandomized, sequential group, dose-escalation study. The following dose cohorts will be evaluated as part of the dose-escalation portion of the study:

CCI [REDACTED] Dosing Cohorts

Cohort 1: CCI [REDACTED]

Cohort 2a: CCI [REDACTED]

Cohort 3: CCI [REDACTED]

Cohort 4a: CCI [REDACTED]

CCI [REDACTED] Dosing Cohorts

Cohort 2b: CCI [REDACTED]

Cohort 4b: CCI [REDACTED]

DLT reviews have occurred for all cohorts and no DLTs were observed. Consequently, no maximum tolerated dose (MTD) has been reached. Expansion of Cohort 2b is described below in the Phase 2 portion of the study. Under Amendment 6 of the protocol, subjects in Cohort 4b CCI [REDACTED] will be transitioned to CCI [REDACTED] (i.e., the dosage of acalabrutinib for Phase 3 studies). Subjects in Cohort 3 had been transitioned to CCI [REDACTED] under Amendment 4 of the protocol, and subjects in Cohorts 1, 2a, and 4a had been transitioned to CCI [REDACTED] under Amendment 5 of the protocol. Any subjects not switched to CCI [REDACTED] will need to be reviewed with the medical monitor.

3.1.2. Expansion Cohorts – Phase 2

Due to the promising safety and efficacy data observed to date on the study, an expansion cohort of CCI [REDACTED] (Cohort 2c) was added under Amendment 4 of the protocol. In support of the planned Phase 3 program for acalabrutinib, Cohort 2b CCI [REDACTED] is being expanded from 30 to approximately 65 subjects to further assess the safety and efficacy of this regimen in subjects with relapsed/refractory CLL/SLL. Therefore, the dosing regimens being evaluated in the Phase 2 portion of this protocol for subjects with previously treated CLL are as follows:

- Cohort 2b is CCI [REDACTED] (N = 65, approximately); this dose level is the planned dosage for Phase 3 studies with acalabrutinib in subjects with CLL.

- Cohort 2c is CCI [REDACTED] (N = 30); under Amendment 6 of the protocol, subjects in Cohort 2c will be transitioned to CCI [REDACTED]

This protocol also includes the following patient subgroups:

Treatment Naive Group: Under Amendment 5, these subjects have been expanded from 60 to 90. This group consists of 90 subjects who are treatment-naive and require treatment for CLL and a) do not want to receive chemoimmunotherapy or b) have comorbidities that would preclude chemoimmunotherapy. The planned dosages for this group are:

- Cohort 7 is CCI [REDACTED] (N = 11 to 30); under Amendment 6 of the protocol, subjects in Cohort 7 were transitioned to CCI [REDACTED]
- Cohort 11 is CCI [REDACTED] (N = 11 to 60)

Ibrutinib Intolerant (Cohort 8): A group of up to 35 subjects who experienced an ibrutinib-related adverse event (AE) and are not tolerating ibrutinib because of the AE. Examples of ibrutinib-related AEs include, but are not limited to, diarrhea, fatigue, arthralgia, rash, peripheral edema, bleeding events, atrial fibrillation, and blurry vision (Byrd 2013, Byrd 2014). These AEs are likely related to off-target effects of ibrutinib including inhibition of epidermal growth factor receptor (EGFR). As described in Section 1.2, acalabrutinib was designed to be a more selective molecule than ibrutinib and as such acalabrutinib has a better preclinical and, to date, clinical safety profile than ibrutinib. Therefore, subjects who did not tolerate ibrutinib may fare better on acalabrutinib. The planned dosage for this group is CCI [REDACTED] based on the safety and PK/PD observed with acalabrutinib CCI [REDACTED] (Section 1.3). This dose regimen has a lower C_{max} of acalabrutinib while providing full BTK occupancy for 24 hours.

Richter's Syndrome/Prolymphocytic Leukemia Transformation Group (Cohort 9):

A group of up to 30 subjects with Richter's syndrome or prolymphocytic leukemia transformation. Richter's syndrome is a transformation from CLL to DLBCL, which occurs in 5% to 10% of patients. The median survival is 4 to 5 months for patients diagnosed with Richter's syndrome (Jandl 1996). Prolymphocytic leukemia transformation is manifested by the presence of > 50% of B-cell prolymphocytes in the peripheral blood and is a more aggressive disease state (Absi 2005). The planned dosage for this group is CCI [REDACTED] based on the safety observed with acalabrutinib CCI [REDACTED]. The CCI [REDACTED] is supported by preliminary results from an ongoing study of acalabrutinib in spontaneous canine lymphoma, which is similar to human DLBCL.

Preliminary results from the canine study showed that BID dosing reversed progression in dogs receiving QD dosing and also produced more durable responses (Gardner 2014). In addition, preliminary results assessing BTK occupancy using a biotin-tagged analogue of acalabrutinib show near complete BTK occupancy over 24 hours with CCI compared with CCI (Section 1.3.2). Therefore, CCI may ensure BTK inhibition for the entire 24 hours including inhibition of any newly synthesized BTK; this may be beneficial in terms of increased efficacy and/or decreased development of resistance to acalabrutinib in aggressive tumors.

Ibrutinib R/R Group (Cohort 10): A group of up to 6 subjects with CLL refractory to or relapsed after ibrutinib therapy when administered per the ibrutinib prescribing information (i.e., CCI). Refractory subjects will be defined as subjects whose best response to ibrutinib was SD after CCI of therapy or did not respond to therapy. Relapsed subjects will be defined as subjects who initially responded to ibrutinib therapy but then developed signs of clinical progression. The planned dosage for this group is CCI based on the safety observed with CCI. As described above, BID dosing may ensure BTK inhibition for the entire 24 hours including inhibition of any newly synthesized BTK; this may be beneficial in terms of increased efficacy with acalabrutinib in comparison with ibrutinib QD.

Treatment with acalabrutinib may be continued for CCI until disease progression or an unacceptable drug-related toxicity occurs. Subjects who meet criteria of disease progression and are continuing to gain clinical benefit from therapy may be able to temporarily remain on acalabrutinib after discussion with the medical monitor. All subjects who discontinue study drug will have a safety follow-up visit 30 (+ 7) days after the last dose of study drug to monitor for resolution or progression of AEs and to document the occurrence of any new events, regardless of whether the subject receives a new anticancer therapy or demonstrates disease progression within this timeframe.

For all cohorts except Cohort 9, radiologic tumor assessment will be done at screening and at the end of Cycle 2, Cycle 4, and Cycle 6, then every 6 cycles until Cycle 36, and then every 12 cycles thereafter. For subjects in Cohort 9, radiologic tumor assessment will be done at screening and at the end of Cycle 2, Cycle 4, Cycle 6, Cycle 9, Cycle 12, Cycle 15, Cycle 18, Cycle 21, Cycle 24, and every 6 cycles thereafter. Otherwise, radiologic tumor assessments are done at investigator discretion. Confirmation of complete response (CR) will require bone marrow analysis and radiologic tumor assessment (as applicable for subjects in Cohort 9). For subjects who remain on study

for > 11 months, a mandatory bone marrow aspirate and biopsy is required in Cycle 12 concurrent with the radiologic tumor assessment.

Note: Under amendment 9 of this protocol, subjects in all cohorts will synchronize their clinic visits and laboratory assessments (excluding the HBV testing that will be every 3 cycles regardless of the imaging/clinic frequency) with the new imaging scheduled visits.

In the event disease progression is suspected due to physical examination or laboratory test, a CT scan must be performed to confirm disease progression. If the sole lesion lies within the field of prior radiotherapy, there must be evidence of disease progression in that lesion.

All subjects will have standard hematology, chemistry, and urinalysis safety panels done at screening. This study also includes pancreatic function assessment (serum amylase and serum lipase) through Cycle 6 due to the pancreatic findings in the 28-day GLP rat toxicity study. This study also includes cardiac troponin testing through Cycle 6 and echocardiograms at screening and at end of Cycle 6. Once dosing commences, all subjects will be evaluated for safety once weekly for the first 4 weeks, every other week for Cycle 2, and monthly thereafter. Blood samples will be collected for PK/PD assessments in Cycle 1. ECGs will be done at screening, and on Day 1-2, 8, 15, 22, 28 of Cycle 1, Day 15 and 28 of Cycle 2, and monthly thereafter through Cycle 6 for a subset of subjects from the dose escalation portion of the study only. ECGs are done in triplicate for screening only. Thereafter, single ECGs are done unless a repeat ECG is required (see [Section 4.1](#) for a more detailed description of ECG assessments).

Note: The Phase 1 portion of the study has been closed, therefore the intensive ECG schedule for the subjects in the dose-escalation cohorts has been completed.

CCI
[Redacted text block]

Refer to [Table 4-1](#) for a comprehensive list of study assessments and their timing.

3.1.3. End of Study

The study duration is approximately 7 years, until final data cutoff (DCO); approximately >5 years, until last subject last visit (LSLV) (total of >12 years).

The final data cutoff (DCO) in support of final database lock will occur approximately 63 cycles after the last subject was administered the first dose of investigational product.

Final data analysis will be performed and a CSR will be written based on the final database lock.

The end of study is defined as the date of the last visit of the last subject in the study.

After the final DCO, the following applies to subjects who are still on treatment and, in the Investigator's opinion, deriving clinical benefit:

- Where acalabrutinib is commercially available and reasonably accessible, subjects will be transitioned off study, and treatment will continue outside of the study protocol, per local laws and regulations.
- Where acalabrutinib is not commercially available or not reasonably accessible, subjects may be re-consented to continue within this study to receive acalabrutinib in line with standards of care through a continued treatment period (managed by the sponsor's Post Analysis and Reporting Team [PART] program) as long as, in the Investigator's opinion, the subject is deriving clinical benefit and has not fulfilled any discontinuation criteria.

After the DCO, all subjects' medical procedures and assessments will continue to be documented in the subject's medical records, but only SAEs will be reported using a paper form. Of the data collected at the study site after the final DCO, only SAEs will be reported.

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

3.2. Study Parameters

3.2.1. Efficacy Parameters

- ORR by investigator assessment
- DOR by investigator assessment
- PFS by investigator assessment

3.2.2. Safety Parameters

- DLTs and MTD
- Frequency, severity, and attribution of AEs

3.2.3. Pharmacokinetic and CCI Parameters

A description of the pharmacokinetic parameters for acalabrutinib and its major metabolite in plasma are provided in [Section 6.4.4](#).

CCI
[Redacted]
[Redacted]
[Redacted]

3.3. Rationale for Study Design and Dosing Regimen

The starting acalabrutinib dose of CCI was selected based on the United States Food and Drug Administration (FDA) Guidance: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers (MSSD), and Nonclinical Evaluation for Anticancer Pharmaceuticals (ICH S9) ([FDA 2005](#), [FDA 2010](#)). Standard GLP 28-day nonclinical systemic toxicity studies in rats and dogs were conducted in support of this trial. The no observable adverse effect level in the dog was 30 mg/kg/day, which was the highest dose evaluated. In rats, 30 mg/kg/day resulted in minimal inflammation of the pancreas in some animals, with reversal, indicating the rat to be the more sensitive preclinical species. The pancreatic effects were minimally increased at 100 mg/kg/day in the rat though there was no clinical evidence of toxicity. Hence, the 100 mg/kg/day was selected to conservatively represent the highest non-severely toxic dose (HNSTD). Following the S9 guidance and using conversion factors from Table 1 in the MSSD guidance, the conversion factor for mg/kg to mg/m² for rodents is 6, which converts to 600 mg/m² in rats. The starting human dose for oncology would be one-tenth the HNSTD, 60 mg/m², CCI
[Redacted]

The Phase 1, dose-escalation portion of the study in subjects with relapsed/refractory CLL was completed. As no DLTs occurred during Phase 1 and escalation beyond CCI was not warranted based on PK results, the Phase 2 expansion portion of the protocol was initiated, as described in [Section 3.1.2](#). To date, all dose regimens evaluated have been well tolerated. No drug-related toxicity had been identified.

3.4. Selection of Study Population

3.4.1. Inclusion Criteria

To be eligible to participate in this study, a subject must meet the following criteria:

1. Men and women ≥ 18 years of age with a confirmed diagnosis of CLL/SLL, which has relapsed after, or been refractory to, ≥ 2 previous treatments for CLL/SLL.

2. Must have measurable CLL/SLL defined as ≥ 1 lymph node ≥ 2 cm as measured in the longest diameter.
3. Active disease meeting ≥ 1 of the following IWCLL 2008 criteria for requiring treatment:
 - a. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia (hemoglobin < 10 g/dL) and/or thrombocytopenia (platelets $< 100,000/\mu\text{L}$).
 - b. Massive (i.e., ≥ 6 cm below the left costal margin), progressive, or symptomatic splenomegaly.
 - c. Massive nodes (i.e., ≥ 10 cm in the longest diameter), progressive, or symptomatic lymphadenopathy.
 - d. Progressive lymphocytosis with an increase of $> 50\%$ over a 2-month period or a lymphocyte doubling time (LDT) of < 6 months. LDT may be obtained by linear regression extrapolation of absolute lymphocyte counts (ALC) obtained at intervals of 2 weeks over an observation period of 2 to 3 months. In subjects with initial blood lymphocyte counts of $< 30 \times 10^9/\text{L}$ ($30,000/\mu\text{L}$), LDT should not be used as a single parameter to define indication for treatment. In addition, factors contributing to lymphocytosis or lymphadenopathy other than CLL (e.g., infections) should be excluded.
 - e. Autoimmune anemia and/or thrombocytopenia that is poorly responsive to standard therapy.
 - f. Constitutional symptoms documented in the subject's chart with supportive objective measures, as appropriate, defined as ≥ 1 of the following disease-related symptoms or signs:
 - i. Unintentional weight loss $\geq 10\%$ within the previous 6 months before Screening
 - ii. Fevers higher than 100.5°F or 38.0°C for 2 or more weeks before Screening without evidence of infection
 - iii. Night sweats for > 1 month before screening without evidence of infection
4. 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 study drug if sexually active and able to bear or beget children (see [Section 3.7.9](#) for list of highly effective methods of contraception).
6. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty.
7. 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 subject privacy regulations).
8. Removed at Amendment 11.

3.4.2. Inclusion Criteria for Treatment Subgroups

Subjects meeting the following criteria will be eligible for the indicated Treatment Subgroups. In addition, Inclusion Criteria 2 to 8 from [Section 3.4.1](#) apply to the Treatment Subgroups as well.

1. **Treatment Naive only:** Men and women ≥ 18 years of age with confirmed diagnosis of CLL/SLL, who require treatment per National Cancer Institute or International Working Group guidelines and a) do not want to receive chemoimmunotherapy or b) have comorbidities that would preclude chemoimmunotherapy.
2. **Ibrutinib Intolerant only:** Men and women ≥ 18 years of age with confirmed diagnosis of CLL/SLL who are not tolerating ibrutinib due to ibrutinib-related AEs.
3. **Richter's Syndrome and Polymphocytic Leukemia Transformation only:** Men and women ≥ 18 years of age with biopsy proven DLBCL Richter's transformation or polymphocytic leukemia transformation.
4. **Ibrutinib R/R only:** Men and women ≥ 18 years of age with confirmed diagnosis of CLL/SLL whose best response after 2 cycles of ibrutinib therapy was SD or nonresponse or who initially responded to ibrutinib therapy and now have signs of clinical progression.

3.4.3. Exclusion Criteria

A subject meeting any of the following criteria will be excluded from this study:

1. Prior malignancy, except for adequately treated basal cell, squamous cell skin cancer or in situ cervical cancer. Subjects with other prior malignancies from which the subject has been disease free for ≥ 2 years may be included if approved by the medical monitor.
2. 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.
3. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or left ventricular ejection fraction (LVEF) $\leq 40\%$.
4. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease, partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass.
5. Any immunotherapy within 4 weeks of first dose of study drug.
6. For subjects with recent chemotherapy or experimental therapy the first dose of study drug must occur after 5 times the half-life of the agent(s).
7. Relapsed after, or refractory to, prior BTK inhibitor therapy (Note: Does not apply to Ibrutinib R/R or Richter's Syndrome Group).

8. Any history of Richter's transformation (Note: Does not apply to Richter's Syndrome Group).
10. Central nervous system (CNS) involvement by lymphoma.
11. Grade ≥ 2 toxicity (other than alopecia) continuing from prior anticancer therapy including radiation.
12. Known history of human immunodeficiency virus (HIV) or serologic status indicating active hepatitis C virus (HCV) or hepatitis B virus (HBV) infection or any uncontrolled active systemic infection. Subjects with hepatitis B core antibody positive who are surface antigen negative or who are hepatitis C antibody positive will need to have a negative PCR result before enrollment. Those who are hepatitis B surface antigen positive or hepatitis B PCR positive and those who are hepatitis C PCR positive will be excluded.
13. Uncontrolled AIHA or ITP defined as declining hemoglobin or platelet count secondary to autoimmune destruction within the screening period or requirement for high doses of steroids (> 20 mg daily of prednisone daily or equivalent).
14. History of stroke or intracranial hemorrhage within 6 months prior to the first dose of study drug.
15. Requires treatment with proton-pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole).
16. Requires anticoagulation with warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon) within 7 days of first dose of study drug.
17. Major surgery within 4 weeks before first dose of study drug.
18. ANC $< 0.75 \times 10^9/L$ or platelet count $< 50 \times 10^9/L$ unless there is bone marrow involvement.
19. Total bilirubin $> 1.5 \times$ ULN (total bilirubin $\leq 2.5 \times$ ULN allowed in subjects with autoimmune hemolytic anemia that is otherwise controlled); AST or ALT $> 3.0 \times$ ULN unless disease related.
20. Serum amylase $> 1.5 \times$ ULN or serum lipase $> 1.5 \times$ ULN.
21. Significant screening ECG abnormalities including 2nd degree AV block type II, 3rd degree block, Grade 2 or higher bradycardia, or QTc ≥ 480 ms.
22. Cardiac troponin I levels above the limit of normal as specified by the manufacturer.
23. Breast feeding or pregnant.
24. History of bleeding diathesis (e.g., hemophilia, von Willebrand disease).
25. Concurrent participation in another therapeutic clinical trial.
26. Estimated creatinine clearance of < 30 mL/min, calculated using the formula of Cockcroft and Gault $[(140 - \text{Age}) \cdot \text{Mass (kg)}] / (72 \cdot \text{creatinine mg/dL})$; multiply by 0.85 if female].
27. Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before screening.

3.4.4. Replacement of Subjects

Subjects who meet any of the following criteria will be replaced:

- Did not receive at least 21 of 28 doses in Cycle 1, unless due to DLT or another safety-related issue
- Did not undergo a DLT assessment at the start of Cycle 2
- Discontinued treatment during Cycle 1 for reasons other than DLT

It is not necessary to replace subjects if ≥ 4 subjects in a cohort have completed Cycle 1 without a DLT.

3.4.5. Enrollment Procedures

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

- Notify the sponsor when a clinically eligible subject is identified to receive current dose level information and ensure availability on study.
- After the subject has signed and dated the Informed Consent Form (ICF), eligibility has been confirmed, and all screening procedures have been completed, and if deemed eligible for entry, the subject can be officially enrolled in the study.
- To enroll a subject, the study center will fax/email a completed Enrollment 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.

Treatment must begin within 10 days after the enrollment form is faxed or emailed to the sponsor.

3.5. Study Drug: Acalabrutinib Hard Gelatin Capsule

3.5.1. Premedications

No premedications are required for administration of acalabrutinib.

3.5.2. Formulation, Packaging, and Storage

Acalabrutinib drug substance and drug product are manufactured according to cGMP and will be provided to the investigational site by Acerta Pharma or a designee.

Acalabrutinib should be stored according to the instructions on the label that is affixed to the package of the drug product. 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 e-mailed or faxed to the sponsor or the sponsor's representative. Refer to the Investigator Brochure for additional information regarding the drug product to be used in this trial.

3.5.3. Administration of Acalabrutinib

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 once or twice daily with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water. Acalabrutinib can be taken with or without meals.

It is recommended that acalabrutinib be taken as close to the scheduled time as possible (preferably within ± 1 hour). However, if a dose is missed, it can be taken up to 3 hours after the scheduled time with a return to the normal scheduled time the following day. If it has been greater than 3 hours, the dose should not be taken and the subject should take the next dose at the next scheduled time. The missed dose will not be made up and must be returned to the site at the next scheduled visit.

3.5.4. Assuring Subject Compliance

Refer to [Table 4-1](#) and [Section 4.1](#) for doses that must be administered in the clinic to comply with predose and postdose PK/PD measurements and /or ECG assessments. For treatments that are taken in the clinic, subjects should take the dose from the drug dispensed for them for that particular time period. All other 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 to the clinic at their next visit. The administrator will review the diary and ask the subject if all of the capsules were administered. Any remaining or returned capsules will be counted and recorded as described in [Section 7.7](#). Returned capsules must not be redispensed to the same subject or to another subject. The study staff will resupply the subject with the correct number of capsules needed for use until the next visit.

3.5.5. Study Treatment Schedule

Subjects will receive study treatment as detailed in [Section 3.5.3](#) and assessments will be performed as outlined in the Schedule of Assessments ([Table 4-1](#)). Subjects with stable disease or tumor response may continue on therapy until disease progression

(radiologic or clinical) or until the investigator considers the study treatment to be no longer tolerable or in the subject's best interest.

Inpatient dose escalation from **CCI** may be allowed on this protocol with discussion and approval from the medical monitor.

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. Use of hematopoietic growth factors is permitted per the American Society of Clinical Oncology (ASCO) guidelines ([Smith 2015](#)).

For subjects considered at risk for tumor lysis syndrome: Administer appropriate hydration and allopurinol or rasburicase per institutional standards prior to initiating treatment.

3.6.2. Prohibited Concomitant Therapy

Any chemotherapy (e.g., bendamustine, cyclophosphamide, pentostatin, or fludarabine), immunotherapy (e.g., rituximab, GA101, alemtuzumab, or ofatumumab), kinase inhibitors (e.g., ibrutinib and idelalisib), bone marrow transplant, experimental therapy, and radiotherapy are prohibited if being used to treat the disease initially under study. Localized, short courses of radiotherapy are allowed for the treatment of lesions unrelated to the disease under study, if approved by the medical monitor. Likewise, other anticancer therapy may be allowed following discussion with the medical monitor. However, high-dose corticosteroids used to treat underlying CLL are not allowed on study.

3.7. Risks Associated with Acalabrutinib Treatment

The following summarizes the experience with acalabrutinib in hematological cancer studies. Full details regarding the clinical safety of acalabrutinib are presented in Sections 5 and 6 of the acalabrutinib Investigator Brochure.

3.7.1. Hemorrhage

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

Subjects 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. As a precaution, it is suggested that acalabrutinib be withheld 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.

3.7.2. Infections

Serious infections, including fatal events, have occurred in clinical studies with acalabrutinib. Subjects should be monitored for signs and symptoms of infection and treated as medically appropriate.

Consider prophylaxis in subjects who are at increased risk for opportunistic infections.

Refer to [Section 3.7.2.1](#) and [Table 4-1](#) for additional information and monitoring guidance for viral hepatitis and [Section 3.7.2.2](#) for additional information and management guidance for signs and symptoms of PML.

3.7.2.1. Hepatitis B Virus Reactivation

Cases of hepatitis B virus (HBV) reactivation have occurred in clinical studies with acalabrutinib. Therefore, subjects with a history of HBV infection should be monitored every 3 months with a quantitative PCR test for HBV DNA. Monitoring every 3 months should continue until 12 months after the last dose of acalabrutinib. Any subject with a rising viral load (above the 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. Insufficient data exist regarding the safety of resuming acalabrutinib in subjects who develop HBV reactivation.

3.7.2.2. Progressive Multifocal Leukoencephalopathy

Cases of progressive multifocal leukoencephalopathy (PML) have occurred in clinical studies with acalabrutinib. Signs and symptoms of PML may include cognitive and behavioral changes, language disturbances, visual disturbances, sensory deficits, weakness, and coordination and gait difficulties.

If PML is suspected, hold further treatment with acalabrutinib treatment until PML is excluded. A diagnostic evaluation may include (but is not limited to):

- Neurologic consultation
- Brain magnetic resonance imaging (MRI)
- Polymerase chain reaction (PCR) analysis for John Cunningham virus DNA in cerebrospinal fluid

If PML is confirmed, permanently discontinue acalabrutinib.

3.7.3. Cytopenias

Grade 3 or 4 events of cytopenias, including neutropenia, anemia, and thrombocytopenia have occurred in clinical studies with acalabrutinib. Monitor blood counts as specified in the schedule of assessments and as medically appropriate. Please refer to [Section 3.11](#) for study drug modification guidance. Subjects with cytopenias should be managed according to institutional guidelines or as clinically indicated.

3.7.4. Second Primary Malignancies

Second primary malignancies, including solid tumors and skin cancers, have been reported in patients treated with acalabrutinib. The most frequent second primary malignancy was skin cancer (basal cell carcinoma). 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. Refer to [Section 5.5](#) for second primary malignancy reporting guidance.

3.7.5. Atrial Fibrillation

Atrial fibrillation or flutter has 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 with supportive care and diagnostic evaluation as clinically indicated.

3.7.6. Reference Safety Information

For the purpose of reporting AEs and serious adverse events (SAEs):

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

3.7.7. Dietary Restrictions

Because acalabrutinib is metabolized by CYP3A (see [Section 3.7.8](#)), subjects should be strongly cautioned against using herbal remedies or dietary supplements (in particular, St John's Wort, which is a potent CYP3A inducer).

Acalabrutinib can be taken without regard to meals.

3.7.8. Drug-drug Interactions

At the systemic exposure levels expected in this study, acalabrutinib inhibition of CYP metabolism is not anticipated.

However, acalabrutinib is metabolized by CYP3A. Concomitant administration of acalabrutinib with a strong CYP3A and P-glycoprotein (P-gp) inhibitor, itraconazole increased exposure by approximately 5-fold. Conversely, concomitant administration of acalabrutinib with a strong CYP3A inducer, rifampin, decreases acalabrutinib exposure and could reduce efficacy. Consequently, the concomitant use of strong inhibitors/inducers of CYP3A (see [Appendix 1](#)) should be avoided when possible.

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 short-term treatment with a moderate CYP3A inhibitor (see [Appendix 1](#)), decrease acalabrutinib dose to **CCI**

Avoid co-administration of strong CYP3A inducers. If a subject requires treatment with a strong CYP3A inducer, increase the acalabrutinib dose to **CCI** during concomitant administration with the strong inducer and return to recommended dose of **CCI** after stopping the strong CYP3A inducer.

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

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 an acalabrutinib dose.

3.7.9. 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 post-menopausal 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.

Highly Effective Methods of Contraception‡

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

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

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

Periodic abstinence[†] (e.g., calendar, ovulation, sympto-thermal, and post-ovulation methods) and withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Female

condom and male condom should not be used together as an effective method of contraception.

†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 IECs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, and post-ovulation methods) and withdrawal 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.

Developmental and reproductive toxicology studies in rats have not identified acalabrutinib-related toxicities for fertility, reproductive success, embryofetal development or embryofetal survival. In rabbits, at dose levels which resulted in maternal toxicities, skeletal variations were associated with reductions in fetal weights. Effects on parturition and post-natal development are pending. For additional details, refer to the acalabrutinib Investigator Brochure.

Subjects should promptly notify the investigator if they, or their partners, become pregnant during this period. Female subjects must also notify the investigator if they become pregnant within 2 days after the last dose of acalabrutinib. If a female subject becomes pregnant during the treatment period, she must discontinue acalabrutinib immediately. Pregnancy in a female subject or a male subject's partner must be reported as described in [Section 5.6](#).

3.7.10. 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 adverse event unless it results in untoward medical effects.

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic case report form (eCRF).

All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

For any subject experiencing an acalabrutinib overdose (ingestion of more than the dose being tested in the cohort), observation for any symptomatic side effects should be instituted, and vital signs, biochemical and hematologic parameters, and ECGs should be followed closely (consistent with the protocol or more frequently, as needed).

Appropriate supportive management to mitigate adverse effects should be initiated. If the overdose ingestion is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered.

3.8. Assessment of Dose Limiting Toxicity

The DLT review period for dose-escalation is over. However, during the dose-escalation portion of the study a DLT was defined as any of the following events unless the adverse event is clearly related to disease progression or the subject's current medical history and associated comorbidities:

1. Any Grade 3 or greater nonhematologic toxicity with the exceptions of alopecia and Grade 3 nausea, vomiting and diarrhea that respond to supportive therapy.
2. The following hematologic toxicities should be considered as DLTs:
 - a. Grade 4 neutropenia lasting more than 5 days.
 - b. Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia with bleeding, or any requirement for platelets transfusion.
 - c. Grade 3 or greater febrile neutropenia (temperature $\geq 38.5^{\circ}\text{C}$).
 - d. Grade 4 anemia, unexplained by underlying disease.
3. Dosing delay due to toxicity for > 7 consecutive days.

3.9. Assessment of QTc Interval Prolongation by Central ECG Testing

Central ECG testing will be used for a subset of subjects from the dose-escalation portion of the study only.

The potential of acalabrutinib to delay cardiac repolarization will be evaluated using ECGs for the measurement of the QTc interval. The study will be carried out in collaboration with a centralized cardiac safety monitoring laboratory that specializes in cardiac monitoring who will provide centralized ECG functions.

Toxicity grading of QTc interval prolongation is defined by the Common Terminology Criteria for Adverse Events (CTCAE) and provided in [Table 3-1](#).

Table 3-1. QTc Toxicity Grading Defined by CTCAE

Grade	Definition
1	QTc 450 to 480 ms
2	QTc 481 to 500 ms
3	QTc \geq 501 ms on at least 2 separate ECGs
4	QTc \geq 501 ms or $>$ 60 ms change from baseline and Torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia
5	Death

Refer to [Section 4.1](#) for instructions on ECG evaluation.

3.10. Stopping Rules

Subjects with stable disease or tumor response may continue on therapy until disease progression (radiologic or clinical) or until the investigator considers the study treatment to be no longer tolerable or in the subject's best interest, whichever occurs first.

Subjects who meet criteria of disease progression and are continuing to gain clinical benefit from therapy may be able to temporarily remain on acalabrutinib after discussion with the medical monitor.

Treatment of subjects with study drug is terminated if:

- Any subject who has objective evidence of disease progression while receiving protocol required study drug should be withdrawn from the study treatment. If there is uncertainty regarding whether there is disease progression, the subject may continue study treatment and remain under close observation (e.g., evaluated at 2- to 4-week intervals) pending confirmation of disease progression. In particular, transient worsening of disease during temporary interruption of study therapy (e.g., for drug-related toxicity, surgery, or intercurrent illness) may not indicate disease progression. In such circumstances, and if medically appropriate, subjects may resume therapy and relevant clinical, laboratory, and/or radiographic assessments should be done to document whether tumor control can be maintained or whether actual disease progression has occurred.
- Toxicity as defined in dose discontinuation portions of the protocol.
- Any subject whose medical condition substantially changes after entering the study should be carefully evaluated by the investigator in consultation with the

medical monitor. Such subjects should be withdrawn from study treatment if continuing would place them at risk.

- Withdrawal from treatment by subject including withdrawal of informed consent.
- Pregnancy in a subject.
- Investigator decision.
- Requires prohibited treatment.
- Study terminated by Sponsor.

3.11. Dosing Delays and Modifications

Clinical judgment should be used to determine appropriate management of the subject during any AE. Temporary interruption or permanent discontinuation of the study drug should be considered if clinically indicated.

Subjects who experience a non-DLT AE resulting in interruption of treatment for ≤ 7 missed days, may restart treatment at the original dose if the abnormality returns to baseline or Grade 1.

Note: Temporary withholding of acalabrutinib for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. Refer to [Section 3.10](#) for more information on assessing disease progression under these circumstances.

3.12. Data and Safety Monitoring

This trial will be monitored in accordance with the sponsor's pharmacovigilance procedures. Adverse events and serious adverse events (SAEs) will be reviewed internally on an ongoing basis to identify safety concerns. Conference calls with the investigators will be conducted, as needed, to discuss study progress, obtain investigator feedback and exchange, and discuss "significant safety events" (i.e., AEs leading to dose reductions, related SAEs, and deaths). In addition, mandatory safety calls will occur before enrollment of subjects into the next dose escalation cohort level.

4. STUDY ACTIVITIES AND ASSESSMENTS

The schedules of events are shown in [Schedule of Assessments](#). 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 outlined. 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 safety laboratory evaluation except hematology, urinalysis and pregnancy testing will be done using the site's local laboratories.

Table 4-1. Schedule of Assessments

	Screening ^a	Cycle 1					Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycles ≥9 ^b (Cohort 9)	Cycles ≥12 ^b (Non-cohort 9)	Follow Up ^c	Continued Access to Study Drug [*]
		Days (± 2)					Day(s) (± 2)		Day(s) (± 2)	Day(s) (± 2)	Day(s) (± 2)	Day(s) (± 2)	Day(s) (± 2)	Day(s) (± 2)	30 days after last dose	
		1	8	15	22	28	15	28	28	28	28	28	28	28		
Informed consent	x															
Confirm eligibility	x															
Medical history	x															
PE ^d /Vital signs ^e /Weight/ B symptoms ^d	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 ^f (dose escalation only)	x	x	x	x	x	x	x	x	x	x	x					
ECG ^f (expansion cohorts)	x															
Echocardiogram [†]	x										x					
Laboratory assessments:																
Urine pregnancy test ^g	x														x	
Hematology ^h	x		x	x	x	x	x	x	x	x	x	x	x	x	x	
Serum chemistry ⁱ	x		x	x	x	x	x	x	x	x	x	x	x	x	x	
Cardiac troponin I [†]	x	x				x		x	x	x	x					
Amylase & Lipase	x	x				x		x	x	x	x					
Hepatitis serology ^u	x															
HBV PCR ^v								x			x [*]	Q3 cycles	Q3 cycles	x		
Urinalysis ^j	x															
T/B/NK/monocyte cell count ^k		x						x				x	x ^y			
Serum Ig ^l		x						x				x	x			x ^{**}
Bone marrow (aspirate and biopsy)												Cycle 12 only & to confirm CR	Cycle 12 only & to confirm CR			

	Screening ^a	Cycle 1					Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycles ≥9 ^b (Cohort 9)	Cycles ≥12 ^b (Non-cohort 9)	Follow Up ^c	Continued Access to Study Drug [*]
		Days (± 2)					Day(s) (± 2)		Day(s) (± 2)	Day(s) (± 2)	Day(s) (± 2)	Day(s) (± 2)	Day(s) (± 2)	Day(s) (± 2)	30 days after last dose	
		1	8	15	22	28	15	28	28	28	28	28	28	28		
												(if applicable ^z)				
CCI		x ^m	x ^m									x ⁿ			x	
Pharmacokinetics ^o		x	x	x	x	x										
Molecular markers ^p	x															
Acalabrutinib dispensed ^q		x	x	x	x	x	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		x
Tumor assessment	x ^r							x ^s		x ^s		x ^s	x ^s	x ^s		
Concomitant medications	x	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

Abbreviations: ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, HBV = hepatitis B virus; Ig = immunoglobulin; IGHV = immunoglobulin heavy-chain variable; mos = months; PCR = polymerase chain reaction; PE = physical examination; QM = every month

Footnotes for ACE-CL-001 Schedule of Study Activities:

- Screening tests should be performed within 10 days before the first administration of study drug, unless otherwise indicated.
- For subjects in Cohort 9, these study visits (including radiographic assessments) will occur every 3 cycles until cycle 24, then every 6 cycles thereafter. For the other cohorts, the study visits and assessments beyond Cycle 6 will occur every 6 cycles, except for CT scans which will occur every 6 cycles until Cycle 36, and then every 12 cycles thereafter. Under amendment 9 of this protocol, subjects in all cohorts will synchronize their clinic visits and laboratory assessments (excluding the HBV testing that will be every 3 cycles regardless of the imaging/clinic frequency) with the new imaging scheduled visits. Any subjects who have not progressed while receiving study drug treatment and are tolerating study drug may continue beyond Cycle 36 and will keep the same scheduled visits.
- A 30-day (+7 days) safety follow-up visit is required when subjects discontinue study drug.
- The screening physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. Symptom-directed physical examinations are done thereafter. B symptoms will be assessed at Cycle 1, Day 1, Cycle 2, Day 15, then at all visits thereafter (excluding the ET visit), and at the safety follow-up visit.
- Vital signs (blood pressure, pulse, respiratory rate, and temperature) will be assessed after the subject has rested in the sitting position.
- 12-lead electrocardiogram (ECG) will be done in triplicate (≥ 1 minute apart) at screening for all subjects. The intensive ECG schedule, which follows, is only for the subjects in the dose escalation portion of the study. The calculated QTc average of the 3 ECGs must be < 480 ms for eligibility. ECGs will be done on Cycle 1 Day 1 and Cycle 1 Day 8, single ECGs are done predose and at 1, 2, 4, and 6 h postdose. The single ECG on Cycle 1 Day 2 is done predose. On Cycle 1 Day 15, Day 22, and Day 28, a single ECG is done 1 h postdose. Starting with Cycle 2 and ending with Cycle 6, a single ECG is done per visit. Subjects should be in supine position and resting for at least 10 minutes before study-related ECGs. Two consecutive machine-read QTc > 500 ms or > 60 ms above baseline require central ECG review.
- Women of childbearing potential only.
- Hematology includes complete blood count with differential and platelet counts sent to a local laboratory.

- i. Serum chemistry: albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid.
- j. Urinalysis: pH, ketones, specific gravity, bilirubin, protein, blood, and glucose.
- k. T/B/NK/monocyte cell count (i.e., CD3, CD4, CD8, CD14, CD19, CD16/56). Testing will be performed on Cycle 1 Day 1; end of Cycles 2/9/15 then every 6 cycles until Cycle 36, and then every 12 cycles thereafter.
- l. Serum immunoglobulin: IgG, IgM, IgA, and total immunoglobulin (if available). Testing will be performed on Cycle 1 Day 1, end of Cycle 2, then every 6 cycles until Cycle 36, and then every 12 cycles thereafter.
- m. CCI samples are drawn predose and 4 hours (\pm 10 minutes) postdose on the days indicated.
- n. CCI samples are drawn predose on the day indicated.
- o. Pharmacokinetic samples for Cycle 1 Day 1 are drawn predose and at 0.25, 0.5, 0.75, 1, 2, 4, 6 and 24 h (before dose on Day 2) postdose. Samples for Cycle 1 Day 8 are drawn predose and at 0.25, 0.5, 0.75, 1, 2, 4, and 6 h postdose. On Cycle 1 Day 15, 22, and 28, a PK sample is drawn predose and the second PK sample must be drawn before (up to 10 minutes before) the ECG acquisition (if applicable), which is 1 h postdose. PK sampling will be done at select centers and on up to 10 subjects per cohort.
- p. Includes, but is not limited to, interphase cytogenetics, stimulated karyotype, CLL FISH panel, IGHV mutational status, Zap-70 methylation, and beta-2 microglobulin levels.
- q. **Acababrutinib: CCI study drug is administered at the site. Therefore, only dispense enough study drug for the days between visits.** Thereafter, starting with the end of Cycle 1, dispense enough bottles for 1 complete cycle for every cycle to Cycle 6, and thereafter as per study required visit interval.
- r. Pretreatment radiologic tumor assessment should be performed within 30 days before the first dose. A computed tomography (CT) scan (with contrast unless contraindicated) is required of the chest, abdomen, and pelvis.
- s. For all cohorts except Cohort 9, radiologic tumor assessments are mandatory at the end of Cycle 2 (-7 days), Cycle 4 (-7 days), Cycle 6 (-7 days), then every 6 cycles until Cycle 36, and then every 12 cycles thereafter. For subjects in Cohort 9, radiologic tumor assessment will be done at screening and at the end of Cycle 2, Cycle 4, Cycle 6, Cycle 9, Cycle 12, Cycle 15, Cycle 18, Cycle 21, Cycle 24, and every 6 cycles thereafter. Otherwise, radiologic tumor assessments are done at investigator discretion. A CT (with contrast unless contraindicated) scan of the chest, abdomen, and pelvis (and any other relevant diseased area such as the neck) is required. Bone marrow biopsy (at 8 to 12 weeks after the response assessment scan) and radiologic assessments are both required for confirmation of a complete response (CR) (as applicable for subjects in Cohort 9). Testing for minimal residual disease will be done on subjects with confirmed CRs. Response assessment for subjects with Richter's syndrome will require either CT scan with contrast (unless contraindicated) or PET-CT (preferred) of the chest, abdomen, and pelvis and any other disease areas. For subjects with Richter's syndrome, confirmation of CR will require PET/CT or CT with bone marrow biopsy, as outlined in [Table 4-5](#). Clinical assessments of tumor response should be done at every visit.
- t. An echocardiogram is required at screening and at the end of Cycle 6 OR with any Grade 3 increase in cardiac troponin I levels.
- u. Hepatitis serology must include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (anti-HBc), and hepatitis C (HCV) antibody. Subjects who are receiving prophylactic intravenous immunoglobulins (IVIg) and have positive HBsAg or anti-HBc must have negative hepatitis B DNA to be eligible. In addition, any subjects testing positive for any hepatitis serology, must have PCR testing (see exclusion criterion #12).
- v. Subjects who are anti-HBc positive (or have a known history of HBV infection) should be monitored every 3 cycles with a quantitative PCR test for HBV DNA and this testing is recommended to continue until 12 months after last dose of study drug. Any subject with a rising viral load (above lower limit of detection) should discontinue acalabrutinib and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B.
- x. For the subjects who require HBV monitoring (see footnote v), HBV PCR testing at Cycle 9 also for all cohorts.
- y. T/B/NK/monocyte cell count testing at Cycle 9 also for all cohorts (see footnote k).
- z. This is not applicable for subjects in Cohort 9 if being followed by PET-CT for response.

* "Continued access to study drug" phase is for subjects who are deriving clinical benefit from acalabrutinib and will continue acalabrutinib treatment per investigator assessment. This phase begins at the data cutoff (DCO) date defined in [Section 3.1.3](#). All monitoring of subjects will be recorded in the subject's medical record per standard clinical practice. Only SAEs will be reported to the sponsor using a paper form.

** Serum immunoglobulin will include IgM and will be done at the discretion of the investigator.

4.1. Description of Procedures

Informed Consent

Screening

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

Medical History

Screening

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 duration of response to these treatments, also will be recorded.

Adverse Events

At all visits

The accepted regulatory definition for an AE is provided in [Section 5.1](#). 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 5.7](#).

Concomitant Medications and Therapy

At all visits

Document all concomitant medications and procedures from within 14 days before the start of acalabrutinib administration through 30 days (+7 days) after the last dose of acalabrutinib.

Confirmation of Eligibility

Screening

Perform all necessary procedures and evaluations to document that the subject meets each eligibility criterion. Screening evaluations must be completed within 10 days before the subject's first dose of acalabrutinib.

Physical Examination & Vital Signs & Weight & B Symptoms

Per Table 4-1

The screening physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes,

ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and lymphatic system.

Symptom-directed physical examinations will be done during the treatment period and at the safety follow-up visits. B symptoms will be assessed at Cycle 1, Day 1, Cycle 2, Day 15, then at all visits thereafter (excluding the ET visit), and at the safety follow-up visit.

Vital signs (blood pressure, heart rate, respiratory rate, and body temperature) will be assessed after the subject has rested in the sitting position. Vital signs and weight will be measured at every visit.

ECOG Performance Status

At all visits

The ECOG performance index is provided in [Appendix 2](#).

Electrocardiogram – Dose Escalation Portion Only

Per [Table 4-2](#)

A centralized cardiac safety monitoring laboratory will be used in this study. The service provider will provide the ECG equipment (12-lead surface), instructions, and training (when requested). At screening, results from the central ECG reader (i.e., 3 ECGs) will be averaged to determine eligibility and must meet the eligibility criteria of $QTc < 480$ ms. Thereafter single ECGs are done at each timepoint. However, if a machine read ECG registers a QTc (either Bazett's or Fredericia's) of ≥ 501 ms or > 60 ms above baseline then a second ECG must be done after 5 minutes. If at any point, a subject experiences a Grade 3 QTc prolongation (i.e., 2 consecutive ECGs taken at least 5 minutes apart with QTc that are both ≥ 501 ms and/or > 60 ms change from baseline), per the machine on site, the dose must be held pending the QTc results from the centralized review. If centralized review confirms both ECG QTc readings are ≥ 501 ms or > 60 ms change from baseline then the subject must be withdrawn from the study. Conversely, if the centralized review shows that both ECG QTc readings are ≤ 500 ms and ≤ 60 ms change from baseline, dosing may be restarted at the same dose level, but missed doses will not be made up.

Also, if a Grade 3 increase in cardiac troponin I occurs in a subject, ECG testing must be done and the ECGs (triplicates taken at least 1 minute apart) must be sent for central review.

Note: The Phase 1 portion of the study has been closed, therefore the intensive ECG schedule for the subjects in the dose-escalation cohorts has been completed.

Table 4-2. ECG Acquisition Times

Study Segment	Day	ECG Acquisition Times
Screening	--	Triplicate at least 1 min apart
Cycle 1	1-2	Single ECG predose, and 1, 2, 4, 6, and 24 h (before Day 2 dose) after 1 st dose; window for ECGs at 1, 2, 4, 6 h is ± 10 min. The 24-h ECG must be predose on Day 2.
Cycle 1	8	Single ECG predose, and 1, 2, 4, and 6 h after 8 th dose; window for ECGs at 1, 2, 4, 6 h is ± 10 min
Cycle 1	15, 22, 28	Single ECG 1 h (± 10 min) postdose
Cycle 2	15, 28	Single ECG anytime during the visit
Cycles 3 to 6	28	Single ECG anytime during the visit

Electrocardiogram – Expansion Cohorts

Screening

Central ECG testing is not required for subjects in the expansion cohorts. Sites can use their own 12-lead ECG machines for the screening ECGs.

Echocardiogram

Screening, end of Cycle 6

An echocardiogram is required at screening. LVEF must be $> 40\%$ for inclusion in the study. Follow-up echocardiograms are required at the end of Cycle 6 or with a Grade 3 increase in cardiac troponin I levels and at the safety follow-up visit.

Urine Pregnancy Test

Screening and safety follow-up visit

Pregnancy tests are required only for women with childbearing potential.

Hematology

Screening, then all visits starting with Cycle 1 Day 8

Hematology studies must include complete blood count (CBC) with differential and platelet counts. Hematology samples done at response assessment timepoints must be done within 7 days of the CT scan. Testing will be performed at the study center's local laboratory listed on the investigator's form FDA 1572.

Chemistry

Screening, then all visits starting with Cycle 1 Day 8

Chemistry must include albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid. If an unscheduled ECG is done at any time, then an electrolyte panel (i.e., calcium, magnesium, and potassium) must be done to coincide with the ECG testing. Testing will be performed at the study center's local laboratory or central clinical laboratory listed on the investigator's form FDA 1572.

Amylase and Lipase

Screening, Cycle 1 Day 1 then Day 28 visits on all cycles starting with Cycle 2 through end of Cycle 6 and as needed

Serum amylase and serum lipase testing will be performed at the study center's local laboratory or central clinical laboratory listed on the investigator's form FDA 1572.

Cardiac Troponin I

Screening, Cycle 1 Day 1 then Day 28 visits on all cycles starting with Cycle 2 through end of Cycle 6

Cardiac troponin testing will be performed at the study center's local laboratory or central clinical laboratory listed on the investigator's form FDA 1572. If a subject experiences a Grade 3 increase in cardiac troponin I, study drug must be held and an echocardiogram AND ECG testing must be done. Per CTCAE criteria, a Grade 3 increase in cardiac troponin I is defined as levels consistent with myocardial infarction as defined by the manufacturer.

Hepatitis B and C Testing

Screening

Hepatitis serology testing must include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), anti-HBc, and HCV antibody. 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. In addition, any subjects testing positive for any hepatitis serology, must have PCR testing (see [Table 4-1](#) and exclusion criterion #12). Testing will be done by local or central laboratory.

Refer to [Section 3.7.2.1](#) and [Table 4-1](#) regarding monitoring of subjects who are anti-HBc positive or have a known history of HBV.

Urinalysis

Screening

Urinalysis includes pH, ketones, specific gravity, bilirubin, protein, blood, and glucose. Testing will be performed at the study center's local laboratory or central clinical laboratory listed on the investigator's form FDA 1572.

T/B/NK/Monocyte Cell Count

Per [Table 4-1](#)

Flow cytometry testing for CD3⁺, CD4⁺, CD8⁺, CD14⁺, CD19⁺, CD16/56⁺ cells. Testing will be performed at the study center's local laboratory or central clinical laboratory listed on the investigator's form FDA 1572.

Serum Immunoglobulin

Per [Table 4-1](#)

Testing for IgG, IgM, IgA and total immunoglobulin (if available) levels. Testing will be performed at the study center's local laboratory or central clinical laboratory listed on the investigator's form FDA 1572.

CCI



Pharmacokinetics

Per [Table 4-3](#)

Refer to the laboratory binder for instructions on collecting and processing these samples. Testing will be performed at a central clinical laboratory. PK testing will only be done at select centers and on a subset of subjects for each cohort (≤ 10 subjects/cohort).

Table 4-3. Pharmacokinetic Sample Schedule

			Hours Postdose							
Cycle	Day	Predose	0.25 (± 1 min)	0.5 (± 5 min)	0.75 (± 5 min)	1 (± 10 min)	2 (± 10 min)	4 (± 10 min)	6 (± 10 min)	24 (± 30 min)
1	1	X	X	X	X	X	X	X	X	X*before Day 2 dose
	8	X	X	X	X	X	X	X	X	
	15, 22, 28	Predose and 1 hour (± 10 minutes)								

Molecular Testing

Screening

Blood will be drawn for molecular testing including, but not limited to, interphase cytogenetics, stimulated karyotype, CLL fluorescence in situ hybridization (FISH) panel, immunoglobulin heavy-chain variable (IGHV) mutational status, ZAP-70, and beta-2 microglobulin levels. Refer to the laboratory binder for instructions on collecting and processing these samples. Testing will be performed at central clinical laboratories.

Bone Marrow

Cycle 12 and to confirm CR

Bone marrow aspirate and biopsy are required to confirm a CR and must be done 8 to 12 weeks following the CT scan (as applicable for subjects in Cohort 9). A repeat bone marrow biopsy in 6 months may be performed to confirm CR in subjects with clinical, laboratory, and radiologic findings supportive of CR but with prior bone marrow biopsy/aspirate showing CLL disease involvement. A mandatory bone marrow aspirate and biopsy are required at the end of Cycle 12 concurrent with the radiologic tumor assessment as outlined below. Testing will be performed at the study center's local laboratory listed on the investigator's form FDA 1572.

Tumor Assessment

Per Table 4-1

Pretreatment tumor assessment should be performed within 30 days (+7 days) before the first dose. A computed tomography (CT) scan with contrast (unless contraindicated) is required of the chest, abdomen, and pelvis and any other diseased area (e.g., the neck) for the pretreatment tumor assessment for subjects. Bone marrow and radiologic assessments are both required for confirmation of a CR, with the exception of subjects

with Richter's syndrome. In addition, 4-color flow cytometry will be used to determine the presence or absence of minimal residual disease (MRD) in subjects who achieve a CR per the response criteria outlined in [Section 4.2](#). Response assessment for subjects with Richter's syndrome will require either CT scan with contrast (unless contraindicated) or PET-CT (preferred) of the chest, abdomen, and pelvis and any other disease areas. For subjects with Richter's syndrome, confirmation of CR will require PET/CT or CT with bone marrow biopsy, as outlined in [Table 4-5](#). The overall efficacy response will assess the response of the underlying malignant transformation.

Study Drug Accountability

Cycle 1 Day 1, 2, 8, 15, 22, and 28, and at every visit

See [Section 7.7](#).

4.2. Investigator's Assessment of Response to Treatment

The investigator must rate the subject's response to treatment based on recent guidelines for CLL and SLL ([Table 4-4](#)) with incorporation of the clarification for treatment-related lymphocytosis ([Cheson 2012](#)). For the Richter's Syndrome, the guidelines for assessing response are provided in [Table 4-5](#); the response assessment for Richter's syndrome will be using PET/CT (preferred) or CT. For all response assessments, hematology samples must be drawn within 7 days of the scan. Bone marrow biopsy done to confirm a complete response must be done at 8 to 12 weeks after the response assessment scan.

Any suspected case of disease progression should be confirmed with a CT scan if one was not obtained, and should be reported to the Sponsor or designee via the electronic data capture (EDC) system within 24 hours of discovery. Subjects may continue study treatment until progression is confirmed by a serial exam at least 2 weeks later.

Subjects who meet criteria of disease progression and are continuing to gain clinical benefit from therapy may be able to temporarily remain on acalabrutinib after discussion with the medical monitor.

Table 4-4. Response Assessment Criteria for CLL/SLL (modified from Hallek 2008)

Response	Lymphocytes	Bone Marrow	Physical Examination^a (Nodes, Liver, Spleen)	Peripheral Blood
CR*	Lymphocytes < 4 x 10 ⁹ /L	Normocellular < 30% lymphocytes No B-lymphoid nodules	Normal (e.g., no lymph nodes > 1.5 cm)	ANC > 1.5 x 10 ⁹ /L ^b Platelets > 100 x 10 ⁹ /L ^b Hemoglobin > 11.0 g/dL (untransfused) ^b
CRi	Lymphocytes < 4 x 10 ⁹ /L	Hypocellular < 30% lymphocytes No B-lymphoid nodules	Normal (e.g., no lymph nodes > 1.5 cm)	Persistent anemia, thrombocytopenia, or neutropenia related to drug toxicity
PR*	Lymphocytes < 5 x 10 ⁹ /L Or ≥ 50% decrease from baseline	Not assessed	≥ 50% reduction in lymphadenopathy ^c and/or in spleen or liver enlargement	ANC > 1.5 x 10 ⁹ /L Or Platelets > 100 x 10 ⁹ /L or ≥ 50% improvement over baseline ^b Or Hemoglobin > 11.0 g/dL or ≥ 50% improvement over baseline (untransfused) ^b
PRL*	Lymphocytes ≥ 5 x 10 ⁹ /L AND <50% decrease from baseline	Not assessed	≥ 50% reduction in lymphadenopathy ^c and/or in spleen or liver enlargement	ANC > 1.5 x 10 ⁹ /L Or Platelets > 100 x 10 ⁹ /L or ≥ 50% improvement over baseline ^b Or Hemoglobin > 11.0 g/dL or ≥ 50% improvement over baseline (untransfused) ^b
SD	Absence of PD and failure to achieve at least a PR			
PD*	Lymphocytes ≥ 50% increase over baseline, with ≥ 5000 B lymphocytes/μL	Not assessed (except to confirm PD as assessed by progressive cytopenias)	Appearance of any new lesion or de novo appearance of hepatomegaly or splenomegaly Or Increase ≥ 50% in lymphadenopathy Or Increase ≥ 50% in hepatomegaly Or Increase ≥ 50% in splenomegaly	Platelets decrease of ≥ 50% from baseline secondary to CLL or less than 100,000/μL and worsening bone marrow Or Hemoglobin decrease of > 2 g/dL from baseline secondary to CLL or decrease to less than 100g/L and worsening bone marrow

Footnotes are on the next page.

Footnotes to [Table 4-4](#)

ANC = absolute neutrophil count; CR = complete remission; CRi = CR with incomplete bone marrow recovery; PD = progressive disease; PR = partial remission (response); PRL = partial remission (response) with lymphocytosis; SD = stable disease.

*CR: all of the above CR criteria have to be met, and subjects have to lack disease-related constitutional symptoms; PR: at least two of the above PR criteria for lymphadenopathy, splenomegaly, hepatomegaly, or lymphocytes plus one of the criteria for ANC, platelets or hemoglobin have to be met; PRL: presence of lymphocytosis, plus $\geq 50\%$ reduction in lymphadenopathy and/or in spleen or liver enlargement, plus one of the criteria for ANC, platelets or hemoglobin have to be met; PD: at least one of the above PD criteria has to be met, or transformation to a more aggressive histology (e.g., Richter's syndrome). For PD as assessed by progressive cytopenias, a bone marrow biopsy is required for confirmation. Note: Isolated elevation of treatment-related lymphocytosis by itself will not be considered PD unless patient becomes symptomatic from this per [Cheson 2012](#).

- a Computed tomography (CT) scan of abdomen, pelvis, and thorax may be used if previously abnormal.
- b Without need for exogenous growth factors.
- c If the sum products of ≤ 6 lymph nodes or in the largest diameter of the enlarged lymph node(s) detected before therapy and no increase in any lymph node or new enlarged lymph nodes.

Table 4-5. Response Assessment Criteria for Richter’s Syndrome (Cheson 2014)

Response and Site	PET-CT-Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on SPST It is recognized that in Waldeyer’s ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, 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 marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† 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	$\geq 50\%$ 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 \times 5 mm as the default value When no longer visible, 0 \times 0 mm For a node > 5 mm \times 5 mm, but smaller than 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
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 PPD progression:
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by $\geq 50\%$ from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by $> 50\%$ of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	New or recurrent splenomegaly New or clear progression of preexisting nonmeasured lesions
Nonmeasured lesions	None	

(continued on following page)

Abbreviations: CR = complete remission, CT = computed tomography, FDG = [¹⁸F]fluorodeoxyglucose, PET = positron-emission tomography, PR = partial remission, SD = stable disease, SPD = sum of the product of the diameters

Table 4-5. Response Assessment Criteria for Richter’s Syndrome (Cheson 2014) (continued)

Table 3. Revised Criteria for Response Assessment (continued)		
Response and Site	PET-CT-Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: SPS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; 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 score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, 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 (eg, 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 (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET SPS: 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

The safety follow-up visit is conducted 30 (+ 7) days after the last acalabrutinib dose to monitor for resolution or progression of AEs and to document the occurrence of any new events or SAEs related to study drug if the AE reporting period ended prior to the safety follow-up visit with the start of new anticancer therapy. Refer to [Table 4-1](#) for the assessments done at these visits. 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 ([Table 4-1](#)) describes the procedures required for the safety follow-up visit.

4.4. 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. 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).

5.1. Definitions

5.1.1. 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.

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 CLL/SLL that were not present before the AE reporting period (see [Section 5.3](#)).
- 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 AEs.

The following are NOT considered an AE:

- **Pre-existing condition that has not worsened:** A pre-existing condition (documented on the medical history CRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study 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 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 done 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 the 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 that 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.

Symptomatic deterioration may occur in some subjects. Symptomatic deterioration is when progression is evident in the subject's clinical symptoms and the investigator may elect not to perform further disease assessments.

If there is any uncertainty about an AE being due only to the disease under study, it should be reported as an AE or SAE.

5.1.2. 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. It does not include an AE that, had it occurred in a more severe form, might have caused death).
- It requires or prolongs in-patient 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 study drug.
- 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 1 of the outcomes listed above).

5.1.3. Severity

Definitions found in the CTCAE version 4.03 (CTCAE v4.03) or higher will be used for grading the severity (intensity) of **nonhematologic** and **hematologic** AEs. The CTCAE v4.03 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any nonhematologic AE not listed in the CTCAE v4.03, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities
- Grade 2 (Moderate AE) – experiences which 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 which are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment
- Grade 4 (Life-threatening or disabling AE) – experiences which cause the subject to be in imminent danger of death
- Grade 5 (Death related to AE) – experiences which result in subject death

5.1.4. Adverse Events of Special Interest

The following events are adverse events of special interest (AESIs) and must be reported to the sponsor expeditiously (see [Section 5.3](#) for reporting instructions), irrespective of regulatory seriousness criteria or causality:

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

5.2. 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 up to the DCO (see [Section 3.1.3](#)), as outlined in the prior sections, are recorded on the electronic CRF (eCRF). After the DCO, only SAEs, overdoses, and pregnancies must be reported; AEs will be recorded in the subject's medical record. All SAEs also must be reported on the SAE paper form (see [Section 5.7](#)).

5.3. Adverse Event Reporting Period

After the signing of the ICF and prior to the first dose of study drug, all SAEs must be reported.

After the first dose of study drug, all AEs/SAEs, irrespective of attribution of causality, must be reported.

All AEs will be reported until 30 days (+7 days) after the last dose of study drug or the start of new anticancer therapy (whichever comes first). After this period, investigators should report SAEs or other AEs of concern that are believed to be related to prior treatment with study drug.

All SAEs which 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.

5.4. Assessment of Adverse Events

Investigators will assess the occurrence of AEs and SAEs at all subject evaluation time points 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 adverse event; however, signs and symptoms of disease progression may be recorded as AEs or SAEs.

Each recorded AE or SAE will be described by its duration (i.e., start and end dates), severity, regulatory seriousness criteria, if applicable, suspected causality to the study drug (see following guidance), and any actions taken. The causality 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 Guidance 2012). Answer Yes or No.

See [Appendix 3](#) for more detail on assessing causality.

5.5. Second Primary Malignancies

Adverse events (AEs) for malignant tumors reported during a study should generally be assessed as serious AEs (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 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 diffuse large B cell lymphoma) should not be considered a new malignant tumor.

5.6. Pregnancy

The investigator should report all pregnancies and pregnancies of the partners of subjects within 24 hours using the Pregnancy Report Form. This form should be sent to the Sponsor Representative. Any pregnancy-associated SAE must be reported using the SAE report form, according to the usual timeline and direction for SAE reporting ([Section 5.7](#)).

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 study medication will be reported, followed to conclusion, and the outcome reported, as long as the subject or partner has consented to participate in follow up.

The 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 miscarriage or any other serious events) must additionally 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 acalabrutinib 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 the Sponsor Representative.

5.7. 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 instructions provided by the sponsor. If electronic SAE/AESI reporting is not available, paper SAE/AESI forms may be sent to the Sponsor Representative. The Sponsor Representative may request follow-up and other

additional information from the investigator (e.g., hospital admission/discharge notes and laboratory results). After final DCO, 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 electronic data capture system. If the primary cause of death is disease progression, the death due to disease progression should not be reported as an SAE. If the primary cause of death is something other than disease progression, then the death should be reported as an SAE with the primary cause of death as the event 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 Representative, 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 study drug (or if a causality assessment is not provided for the SAE, in which case a default of 'related' may be used for expedited reporting purposes) and the SAE is not listed in the current Investigator Brochure (i.e., an unexpected event). In this case, Acerta Pharma 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.

5.8. 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 subject as stable, a new anticancer therapy is initiated, or the subject is lost to follow-up or withdraws consent.

5.9. Hy's Law

Cases where a subject shows elevations in liver biochemistry may require further evaluation, and occurrences of AST or ALT $\geq 3 \times \text{ULN}$ together with total bilirubin $\geq 2 \times \text{ULN}$ may need to be reported as SAEs. Refer to [Appendix 4](#) for further instruction on cases of increases in liver biochemistry and evaluation of Hy's law.

6. STATISTICAL METHODS OF ANALYSIS

6.1. General Considerations and Determination of Sample Size

No formal statistical tests of hypotheses will be performed. Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions for discrete variables) will be used to summarize data as appropriate.

The design of the Phase 1 (i.e., dose-escalation portion) of the study is specified because of its practical simplicity, use of a biomarker, and not because of power considerations. The MTD is defined as the largest daily dose for which < 33% of the subjects experience a DLT during Cycle 1. The MTD was not reached in this study as PK data suggested a plateau in exposure between 250 and 400 mg.

The Phase 2 (expansion portion) of the study will test the null hypothesis that the ORR is $\leq 10\%$ against the alternative hypothesis that it is $\geq 35\%$. Using Simon's optimal 2-stage design (Simon 1989), a total sample size of 30 subjects per cohort has power = 0.90 to achieve a 1-sided significance level of ≤ 0.025 . In Stage 1, 11 subjects will be enrolled per cohort; if ≥ 2 subjects (18%) achieve an objective response of a PR/PRL or better within the first 4 cycles of treatment, then that cohort will continue to full enrollment. Under the Simon design, an ORR of $\geq 23\%$ (i.e., ≥ 7 subjects responding of 30 subjects evaluated) will achieve a significance level of ≤ 0.025 . Using an exact binomial confidence interval (CI), an ORR of 23% (i.e., 7 subjects responding of 30 subjects evaluated) will achieve a 2-sided 90% lower bound of 11.5%.

Considering the planned expansion cohort size of 30 subjects, Table 6-1 shows the 2-sided exact 90% binomial CIs on the true response rate for the range of possible values for the observed response rate.

Table 6-1. Two-Sided Exact 90% CIs for ORR in Expansion Cohorts (N = 30)

Responses, n	Response Rate, %	90%CI	
		Lower Bound	Upper Bound
0	0%	0.0%	9.5%
1	3.3%	0.2%	14.8%
2	6.7%	1.2%	19.6%
3	10.0%	2.8%	23.9%
4	13.3%	4.7%	27.9%
5	16.7%	6.8%	31.9%
6	20.0%	9.1%	35.7%
7	23.3%	11.5%	39.4%
8	26.7%	14.0%	43.0%

Abbreviation: CI=confidence interval, ORR = overall response rate

In addition, the Phase 2 portion of this protocol increases sample size of the CCI cohorts (R/R CLL N = 65 approximately; treatment-naive CLL, N = 60) to provide safety and efficacy data in support of the Phase 3 program of acalabrutinib in CLL. Therefore, depending on the number of subjects enrolled in each expansion cohort approximately 286 evaluable subjects will be enrolled in this study.

6.2. Definition of Analysis Populations

- **Enrolled population:** All subjects who complete the enrollment procedures as specified in the Enrollment Procedures section ([Section 3.4.5](#)) of the protocol.
- **All-treated population:** All 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 drug.

The safety analyses will be performed on the All-treated population. Primary efficacy analyses for ORR and DOR will be based on the efficacy-evaluable population and will be assessed by investigators. PFS analysis will be based on the all-treated population and will be assessed by investigators.

6.3. Missing Data Handling

No imputation of values for missing data will be performed except for missing or partial start and end dates for adverse events and concomitant medication will be imputed according to prespecified, conservative imputation rules. Subjects lost to follow-up (or drop out) will be included in statistical analyses to the point of their last evaluation.

6.4. Endpoint Data Analysis

6.4.1. Safety Endpoint

Safety summaries will include summaries in the form of tables and listings. The frequency (number and percentage) of treatment emergent adverse events will be reported in each treatment group by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term. Summaries will also be presented by the severity of the adverse event 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.

Vital signs, ECGs, and physical examinations will be tabulated and summarized.

6.4.2. Demographics and Baseline Characteristics

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

6.4.3. Analysis of Efficacy Parameters

The following methods will be applied to the investigator assessments:

Overall Response Rate

The point estimate of the ORR will be calculated. The corresponding 95% confidence interval also will be derived.

Duration of Response

The duration of response is measured from the time measurement criteria are met for CR, PR, or PRL (whichever is first recorded) until death or progressive disease is objectively documented. Kaplan-Meier methodology will be used to estimate event-free curves and corresponding quantiles (including the median).

Progression-free Survival

PFS is measured from the time of first study drug administration until death or progressive disease is objectively documented. Kaplan-Meier methodology will be used to estimate the event-free curves and corresponding quantiles (including the median).

CCI

6.4.4. Analysis of Pharmacokinetic / CCI Parameters

The plasma PK of acalabrutinib and a metabolite will be characterized using noncompartmental analysis. The following PK parameters will be calculated, whenever possible, from plasma concentrations of acalabrutinib:

- AUC_{0-last} Area under the plasma concentration-time curve calculated using linear trapezoidal summation from time 0 to time last, where “last” is the time of the last measurable concentration.

- AUC_{0-12} Area under the plasma concentration-time curve from 0 to 12 hours, calculated using linear trapezoidal summation.
- AUC_{0-24} Area under the plasma concentration-time curve from 0 to 24 hours, calculated using linear trapezoidal summation.
- $AUC_{0-24calc}$ area under the concentration-time curve, from time 0 to 24 hour timepoint, calculated by doubling the value for AUC_{0-12}
- AUC_{0-inf} Area under the plasma concentration-time curve from 0 to infinity, calculated using the formula: $AUC_{0-inf} = AUC_{0-last} + C_{last} / \lambda_z$, where λ_z is the apparent terminal elimination rate constant.
- C_{max} Maximum observed plasma concentration
- T_{max} Time of the maximum plasma concentration (obtained without interpolation)
- $t_{1/2}$ Terminal elimination half-life (whenever possible)
- λ_z Terminal elimination rate constant (whenever possible)
- CL/F Oral clearance
- V_z/F Oral volume of distribution

Missing dates or times may be imputed for PK and **CCI** 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 **CCI** sampling for a given subject is not performed according to protocol instructions that subject may be excluded from the PK and **CCI** analyses.

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

CCI
[REDACTED]

7. STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

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

- Unsatisfactory subject enrollment with regard to quality or quantity

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

7.1. Regulatory and Ethical Compliance

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

7.2. Institutional Review Board and Independent Ethics Committee

The investigator will submit this protocol, the informed consent, Investigator Brochure, and any other relevant supporting information (e.g., all advertising materials) to the appropriate IRB for review and approval before study initiation. A signed protocol approval page; a letter confirming IRB approval of the protocol and informed consent; and a statement that the IRB is organized and operates according to Good Clinical Practice (GCP) and the applicable laws and regulations; **must** be forwarded to Acerta Pharma **before** screening subjects for the study. Additionally, sites must forward a signed FDA 1572 form (Statement of Investigator) to Acerta Pharma before screening subjects for study enrollment. Amendments to the protocol must also be approved by the IRB and 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-approved informed consent must be forwarded to Acerta Pharma for regulatory purposes. The investigator, or designee (designee must be listed on the Study Personnel Responsibility/Signature Log, see [Section 7.12](#)), **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 informed consent before enrollment into this study. In the case of a subject who is incapable of providing informed consent, the investigator (or

designee) must obtain a signed and dated informed consent form from the subject's legal guardian. Signed consent forms must remain in each subject's study file and be available for verification by study monitors at any time.

In accordance to individual local and national subject 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 Acerta Pharma and its designees, regulatory agencies, and IRBs. As the study sponsor, Acerta Pharma 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. Subject Screening Log

The investigator **must** keep a record that lists **all** subjects considered for enrollment in the study. For those subjects subsequently excluded from enrollment, record the reason(s) for exclusion.

7.5. Case Report Forms

Authorized study site personnel (see [Section 7.12](#)) 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. The investigator will ensure that source documents that are required to verify the validity and completeness of data transcribed on the eCRFs are never obliterated or destroyed.

7.6. Study Monitoring Requirements

Representatives of Acerta Pharma 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.

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, representatives of Acerta Pharma, 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.

7.7. Investigational Study Drug Accountability

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

Acalabrutinib accountability records must be maintained and readily available for inspection by representatives of Acerta Pharma and are open to inspections by regulatory authorities at any time.

Each shipment of acalabrutinib will contain a Clinical Supplies Shipping Receipt Form (CSSF). Contents of each shipment must be visually inspected to verify the quantity and document the condition of acalabrutinib. The person receiving the shipment and inspecting it must respond to the Drug Depot's e-mail. A copy of the signed and dated CSSF must be emailed to Acerta Pharma at the email address listed on the form; this completed form should be filed in the pharmacy binder.

Additionally, a Drug Re-order Form for requesting more acalabrutinib is provided in the pharmacy binder. If it is used, then the Drug Re-order Form must also be filed with the site's drug accountability records.

A Study 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-CL-001)
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 study drug disposal/destruction to ensure that it complies with Acerta Pharma's requirements. If the site cannot meet Acerta Pharma's requirements for disposal/destruction, arrangements will be made between the site and Acerta Pharma or its representative, for return of unused study drug. 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.

7.8. 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 approval letters, signed ICFs, drug accountability records, SAE forms transmitted to Acerta Pharma, subject files (source documentation) that substantiate entries in eCRFs, 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 Acerta Pharma and obtain written approval from Acerta Pharma before destroying any clinical study records at any time. Acerta Pharma will inform the investigator of the date that study records may be destroyed or return to Acerta Pharma.

Acerta Pharma must be notified in advance of, and Acerta Pharma 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 Acerta Pharma 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.

7.9. Protocol Amendments

Acerta Pharma coordinate any change to the protocol in a protocol amendment document. The amendment will be submitted to the IRB 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 approval must be received by Acerta Pharma 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.

7.10. Publication of Study Results

Authorship, in general, will follow the recommendations of the [International Committee of Medical Journal Editors \(ICMJE 2014\)](#).

7.11. Clinical Trial Insurance

Clinical trial insurance has been undertaken 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.

7.12. General Investigator Responsibilities

The principal investigator must ensure that:

1. He or she will personally 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 permission to use protected health information are obtained from each subject before conducting nonstandard of care study procedures. 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 be collected from the subject.
6. The consent process is conducted in compliance with all applicable regulations and privacy acts.
7. The IRB 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.
9. Any significant protocol deviations are reported to Acerta Pharma and the IRB according to the guidelines at each study site.

10. eCRF pages are completed promptly.
11. All Safety Reports are submitted promptly to the IRB.
12. All SAEs are reported to the Sponsor Representative within 24 hours of knowledge and to the IRB per their requirements.

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Appendix 1 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
cobicistat ^a	ciprofloxacin
conivaptan ^a	clotrimazole
danoprevir and ritonavir ^b	crizotinib,
diltiazem ^a	cyclosporine
elvitegravir and ritonavir ^b	dronedarone ^a
grapefruit juice	erythromycin
idelalisib	fluconazole
indinavir and ritonavir ^b	fluvoxamine
itraconazole ^a	imatinib
ketoconazole,	tofisopam
lopinavir and ritonavir ^{a,b}	verapamil ^a
nefazodone	
nelfinavir ^a	
paritaprevir and ritonavir and (ombitasvir and/or dasabuvir) ^b	
posaconazole	
ritonavir ^{a, b}	
saquinavir and ritonavir ^{a, b}	
telaprevir ^a	
tipranavir and ritonavir ^{a, b}	
troleandomycin	
voriconazole	

- a. Inhibitor of P-glycoprotein.
- b. Ritonavir is usually given in combination with other anti-HIV or anti-HCV drugs in clinical practice. Caution should be used when extrapolating the observed effect of ritonavir alone to the effect of combination regimens on CYP3A activities.
- c. After discontinuation of the strong CYP3A inhibitor, wait 3 days before resuming acalabrutinib.

Strong Inducers of CYP3A	Moderate inducers of CYP3A
carbamazepine	bosentan
enzalutamide	efavirenz
mitotane	etravirine
phenytoin	modafinil
rifampin	
St. John's wort ^a	

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

P-gp Inhibitors	BCRP Inhibitors	Narrow Therapeutic Index P-gp Substrates
amiodarone	curcumin	digoxin
carvedilol	cyclosporine A	everolimus
clarithromycin	eltrombopag	sirolimus
dronedarone		
itraconazole		
lapatinib		
lopinavir and ritonavir		
propafenone		
quinidine		
ranolazine		
ritonavir		
saquinavir and ritonavir		
telaprevir		
tipranavir and ritonavir		
verapamil		

Source: FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Web link Accessed 18 July 2018:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#inVivo>

Bile Acid Sequestrants	Proton Pump Inhibitors	H2-Receptor Antagonists
cholestyramine	dexlansoprazole	cimetidine
colestipol	esomeprazole	famotidine
colesevelam	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/guidancecomplianceregulatoryinformation/lawsactsandrules/ucm428333.pdf>

Appendix 2 ECOG Performance Status

<u>Grade</u>	<u>ECOG</u>
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, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

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

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

Appendix 3 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 preclinical 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 4 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 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 Ceruleplasmin 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 5 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 Acerta Pharma 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 COVID19.

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-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/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.