PROTOCOL

TITLE:	A Phase 1/2 Proof-of-Concept Study of the Combination of ACP-196 and ACP-319 in Subjects with B-cell Malignancies
PROTOCOL NUMBER:	ACE-LY-001
STUDY DRUGS:	Acalabrutinib (ACP-196) and ACP-319
IND NUMBER:	118717
SPONSOR MEDICAL MONITOR:	PPD
SPONSOR:	Acerta Pharma BV Kloosterstraat 9 5349 AB Oss The Netherlands
PROTOCOL DATE:	Version 0.0 – 06 September 2014
AMENDMENT 1 DATE:	Version 1.0 – 05 November 2015
AMENDMENT 2 DATE:	Version 2.0 – 22 January 2016
AMENDMENT 3 DATE:	Version 3.0 – 09 May 2016
AMENDMENT 4 DATE:	Version 4.0 – 20 December 2016
AMENDMENT 5 DATE:	Version 5.0 –11 December 2018
AMENDMENT 6 DATE:	Version 6.0 – 12 February 2020

PROTOCOL APPROVAL

Version 6.0

I have carefully read Protocol ACE-LY-001 entitled “A Phase 1/2 Proof-of-Concept Study of the Combination of ACP-196 and ACP-319 in Subjects with B-cell Malignancies”. I agree to conduct this study as outlined herein and in compliance with Good Clinical Practices (GCP) and all applicable regulatory requirements. Furthermore, I understand that the sponsor, Acerta Pharma BV (Acerta Pharma), and the IRB/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.

Principal Investigator’s Signature Date

Print Name

SUMMARY OF AMENDMENT 6

This protocol is being amended to update the document to reflect updates to the acalabrutinib Investigator Brochure (V8.1, 25 Sep 2019). Under this amendment, all ongoing subjects continued on acalabrutinib monotherapy (these subjects had been discontinued from acalabrutinib + ACP-319 combination therapy) and thus, reference to ACP-319 was removed from the background and other sections of the protocol. Clarifying edits and typographical changes were made throughout the protocol.

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

Change	Rationale
Study Synopsis	Updated to reflect changes in protocol.
Section 1.0 Background Information	Updated to reflect Calquence approval in the United States for the treatment of mantle cell lymphoma who have received at least one prior line of therapy, chronic lymphocytic leukemia, and small lymphocytic lymphoma.
Section 3.0 Study Design	Added details to transition ongoing subjects to a rollover or safety extension study to ensure treatment continuation.
Section 3.2 Rationale for Study Design and Dosing Regimen	Removed previous content and updated to refer the reader to Protocol Amendment 5.0.
Section 3.8.2 Dose Modification and Discontinuation	Removed reference to ACP-319.
Section 3.9 Management of Specific AEs	Removed reference to ACP-319.
Section 3.9.2 Elevated Liver Function Tests and Immune-Mediated Hepatitis	Added monitoring for increases in liver biochemistry, including potential Hy's law or Hy's law, with reference to Appendix 6.
Section 3.10.2, 3.11.3, and Appendix 3	Updated language for concomitant use of strong inhibitors/inducers of CYP3A.
Section 3.10.2 Prohibited or Restricted Concomitant Therapy	Removed reference to ACP-319.
Section 3.11 Risks Associated with Study Drugs	Updated to reflect updated risks per the Investigator Brochure Version 8.1; removed risks associated with ACP-319 monotherapy and acalabrutinib and ACP-319 combination therapy.

Change	Rationale
Section 3.11.3 Drug-Drug Interaction, Section 3.11.4 Reproductive Toxicity, Section 3.11.5 Overdose Instructions, Section 3.12 Withdrawal of Subjects from Study Treatment	Removed reference to ACP-319.
Section 3.11.4 Reproductive Toxicity	Updated to reflect updated Investigator Brochure Version 8.1.
Section 3.11.6 Hepatitis B Virus Reactivation Section 3.11.7 Progressive Multifocal Leukoencephalopathy	These sections were removed from Section 3.11.1 Risks Associated with Acalabrutinib Treatment; however, the sections were moved to another section in the protocol to include additional monitoring guidance.
Section 4.0 Study Activities and Assessments	Updated to remove reference to Appendix 7 schedule of assessments (combination therapy).
Section 6.2.4 Adverse Events of Special Interest	Added Section 6.2.4 Adverse events of special interest to include “ventricular arrhythmias”.
Section 6.3.1 Adverse Event Reporting Period	Updated AE reporting language for consistency across all acalabrutinib protocols.
Section 6.3.3 Malignant Tumors	Added Section 6.3.3 for guidance on reporting of malignant tumors.
Appendix 3 and Appendix 4	Combined into 1 appendix.
Appendix 6 and Appendix 7	Removed schedule of assessments for combination therapy (previous Appendix 6) since it is no longer being administered. Previous Appendix 7 (acalabrutinib monotherapy schedule of assessments) was renumbered as Appendix 5.
Appendix 6	Added appendix for the process to be followed to identify and report potential Hy’s law and Hy’s law cases.

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ABBREVIATIONS

Term	Definition
λ_z	terminal elimination rate constant
ACP-196	acalabrutinib
AE	adverse event
ALC	absolute lymphocyte count
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HBc	hepatitis B core antibody
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
$AUC_{0\text{-last}}$	area under the plasma concentration-time curve from time 0 to time last, calculated using trapezoidal summation, where “last” is the time of the last measurable concentration (C_t)
$AUC_{0\text{-inf}}$	area under the plasma concentration-time curve from time 0 to infinity, calculated using the formula: $AUC_{0\text{-inf}} = AUC_{0\text{-last}} + C_{last} / \lambda_z$, where λ_z is the apparent terminal elimination rate constant
$AUC_{0\text{-12}}$	area under the plasma concentration-time curve, from time 0 to 12 hours, calculated using trapezoidal summation
$AUC_{0\text{-24calc}}$	area under the plasma concentration-time curve, from time 0 to 24 hours, calculated by doubling the value for $AUC_{0\text{-12}}$
AV	atrioventricular
B-ALL	B-cell acute lymphoblastic leukemia
BID	twice daily
BTK	Bruton tyrosine kinase
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CL/F	oral clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed plasma concentration
CMV	cytomegalovirus
CR	complete response
CT	computed tomography

Term	Definition
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
EBMT	European Group for Blood and Marrow Transplant
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
FDA	Food and Drug Administration
FDG	[^{18}F]fluorodeoxyglucose
FL	follicular lymphoma
FLC	free light chains
FSH	follicle stimulating hormone
GCB	germinal center B-cell subtype
GCP	Good Clinical Practices
GI	gastrointestinal
GGT	gamma-glutamyl transpeptidase
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
ICF	informed consent form
IEC	independent ethics committee
Ig	immunoglobulin
IHC	immunohistochemistry
IMWG	International Myeloma Working Group
iNHL	indolent NHL
INR	international normalized ratio
IRB	institutional review board
IVIG	intravenous immunoglobulin
LDH	lactate dehydrogenase
LDi	longest transverse diameter of a lesion
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
MR	minor response
MTD	maximum tolerated dose

Term	Definition
nCR	near complete response
NHL	non-Hodgkin lymphoma
NK	natural killer (cells)
non-GCB	non-germinal center B-cell subtype
nPR	nodular partial remission
ORR	overall response rate
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
P-gp	P-glycoprotein
PI3Kδ	phosphatidylinositol 3-kinase p110-delta
PD	pharmacodynamics
PET	positron-emission topography
PJP	*Pneumocystis jirovecii* pneumonia
PK	pharmacokinetics
PLT	platelet count
PMBCL	primary mediastinal large B-cell lymphoma
PML	progressive multifocal leukoencephalopathy
PR	partial remission (response)
PRL	partial remission (response) with treatment-induced lymphocytosis
PT	prothrombin time
QD	once daily
SAE	serious adverse event
sCR	stringent complete response
SD	stable disease
SDi	shortest axis perpendicular to the longest transverse diameter of a lesion
SFLC	serum-free light chains
SFU	safety follow-up
SIFE	serum immunofixation electrophoresis
SLL	small lymphocytic lymphoma
SPEP	serum protein electrophoresis
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal elimination half-life
TBD	to be determined

Term	Definition
T_{max}	time to maximum plasma concentration
TT	treatment termination
UIFE	urine immunofixation electrophoresis
ULN	upper limit of normal
UPEP	urine serum protein electrophoresis
Vz/F	oral volume of distribution
WHO	World Health Organization
WM	Waldenström macroglobulinemia
WOCBP	women of childbearing potential

STUDY SYNOPSIS

Protocol Number:	ACE-LY-001
Study Drugs:	Acalabrutinib (also known as ACP-196) and ACP-319
Protocol Title:	A Phase 1/2 Proof-of-Concept Study of the Combination of ACP-196 and ACP-319 in Subjects with B-cell Malignancies
Phase:	Phase 1/2
Comparator:	None
Background and Rationale for Study	Through decades of clinical experience, the use of multidrug regimens has been shown to produce higher complete remission (CR) rates and more durable responses, resulting in improved survival in most oncology indications. However, these benefits are often outweighed with the increased toxicity associated with multidrug regimens. This high risk-benefit ratio limits the use of many effective multidrug regimens in elderly patients or patients with comorbid conditions. The advent of highly selective, targeted agents such as Bruton tyrosine kinase (BTK) and phosphatidylinositol 3-kinase p110-delta (PI3Kδ) inhibitors has changed the risk-benefit paradigm traditionally associated with cytotoxic chemotherapy regimens. Small molecule inhibitors of BTK and PI3Kδ produce high overall response rates (ORRs) with few drug-related toxicities in patients with B-cell malignancies. For example, ibrutinib, a first-generation oral, small molecule BTK inhibitor, has been approved for the treatment for chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL; IMBRUVICA [prescribing information] 2014). In addition, ibrutinib has shown clinical efficacy in other non-Hodgkin lymphoma (NHL) histologies, including follicular lymphoma (FL; Advani et al. 2012), diffuse large B-cell lymphoma (DLBCL; De Vos et al. 2013), and in Waldenström macroglobulinemia (WM; Treon et al. 2013). Preliminary data suggests that patients with multiple myeloma (MM) with high BTK activity, as evidenced by phosphorylated BTK, may be particularly responsive to BTK inhibitor therapy (Liu et al. 2014). In preclinical studies, BTK inhibition significantly reduced MM cell growth and tumor-induced osteolysis in a murine model (Tai et al. 2012). Idelalisib, a small molecule PI3Kδ inhibitor, was recently approved for treatment of relapsed CLL in combination with rituximab and third-line treatment of FL and small lymphocytic lymphoma (SLL; ZYDELIG [prescribing information] 2014). Idelalisib has shown an ORR of 57% (51% PR and 6% CR) in a Phase 2 study in subjects with previously treated indolent NHL (iNHL; Gopal et al. 2014). Despite these significant advances, the investigation of additional treatment regimens is essential to improve outcomes in B-cell malignances. A low

	proportion of patients achieve CR when treated with single-agent BTK or PI3Kδ inhibitors compared with conventional chemotherapy or chemoimmunotherapy regimens. Moreover, the median duration of response can be brief (<12 months) in aggressive histologies. The question remains as to whether "targeted combination" therapy can produce more durable responses and potentially more CRs than single agents without an associated increase in toxicity. Certainly, recent clinical data from a Phase 1 and 2 trial of combined treatment with dabrafenib, a selective BRAF inhibitor, and trametinib, a selective mitogen-activated protein kinase (MAPK) kinase (MEK) inhibitor in melanoma suggests this promise may be fulfilled. The combination, when compared with dabrafenib monotherapy, produced statistically significant greater progression-free survival, ORR, and median duration of response without an increase in toxicities (Flaherty et al. 2012). Preclinical models have demonstrated the potential for synergy between the PI3Kδ and BTK pathways. PI3Kδ is thought to activate BTK; however, data from PI3Kδ$^{-/-}$ mice show that activation of BTK through the B-cell receptor (BCR) does not require PI3Kδ (Suzuki et al. 2003). Mice deficient in PI3Kδ and BTK have more profound B-cell defects than either single-mutant mouse strain. In addition to mediating B-cell activation, PI3Kδ and BTK independently down-regulate the expression and function of forkhead box protein O1 (FOXO1) through various mechanisms (Hinman et al. 2007). FOXO1 is a transcription factor for pro-apoptotic and antimitogenic genes, and PI3Kδ and BTK are thought to mediate BCR-induced proliferation and survival in part by down-regulating FOXO1. In addition, nonclinical and clinical data have demonstrated that BTK inhibition alters B-cell recirculation patterns, removing lymphoma cells from protective microenvironment niches and potentially removing them from proximal growth signals (Smith et al. 2015a). Inhibition of BTK and PI3Kδ may also have direct effects on the nonmalignant cells within the tumor microenvironment (López-Herrera et al. 2014). Thus, dual inhibition of BTK and PI3Kδ in patients with B-cell malignancies may ultimately increase the proportion of patients with CRs by promoting apoptosis in malignant B cells through multiple mechanisms. Dual pathway inhibition may increase response durations, due to reduced opportunity for mechanistic resistance (i.e., resistance-conferring mutations would be required in both pathways). Anecdotal reports emerging from clinical studies of ibrutinib and idelalisib suggest that some patients who fail to respond to one kinase inhibitor can subsequently respond well to the other. These early observations may indicate a lack of cross resistance for these signaling pathways. Strong clinical and mechanistic rationale exist to expect increased efficacy with dual inhibition of BTK and PI3Kδ.

	Based on known pathway-related side effects, improved activity may be achievable without a worsening toxicity profile. If so, this dual inhibition approach may improve outcomes for difficult-to-treat patients, including frail or elderly patients and individuals with comorbidities. If activity is sufficiently high, dual inhibition of BTK and PI3Kδ may be an attractive approach to avoid or delay use of cytotoxic chemotherapy regimens in treatment-naive patients with B-cell malignancies. Acerta Pharma BV (Acerta Pharma) is developing a potent, highly selective covalent BTK inhibitor, acalabrutinib (also known as CALQUENCE®). CALQUENCE® has been approved in the United States and other markets for the treatment of adult patients with MCL who have received at least one prior line of therapy, CLL, and SLL. CCI This proof-of-concept study will assess the clinical potential of a dual inhibition approach by evaluating the safety, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy acalabrutinib and ACP-319 in B-cell malignancies.
Study Design:	This study is a multicenter, open-label, nonrandomized, sequential group, dose-escalation study to be conducted at approximately 30 sites. The study is divided into 2 parts: Part 1 of the study is the dose-escalation portion and Part 2 allows for possible expansion groups (Figure 3-1). A cycle is defined as a period of 28 days. **Part 1** In each dose-escalation cohort, subjects will take acalabrutinib and ACP-319 twice daily (BID) at approximately 12-hour intervals. The acalabrutinib dose will be fixed at 100 mg BID. The ACP-319 dose will be escalated as follows: ☐ Cohort 1: Acalabrutinib 100 mg BID + ACP-319 25 mg BID continuously ☐ Cohort 2: Acalabrutinib 100 mg BID + ACP-319 50 mg BID continuously ☐ Cohort 3: Acalabrutinib 100 mg BID + ACP-319 100 mg BID continuously Each dosing cohort will be enrolled sequentially with 6 subjects per cohort. If ≤1 dose-limiting toxicity (DLT) (see below for definition) is observed in the cohort during Cycle 1, escalation to the next cohort will proceed. If ≥2 DLTs are observed during Cycle 1, dosing at that dose and higher will be suspended and the maximum tolerated dose (MTD) will be established as the previous cohort. The MTD is defined as the highest daily dose for which fewer than 33% of the subjects experience a DLT

	during Cycle 1. Escalation will end with Cohort 3 or sooner if the MTD is reached in an earlier cohort. Part 1 of the study will include adult subjects with the following disease types: □ Non-germinal center B-cell subtype (non-GCB) diffuse large B-cell lymphoma (DLBCL), characterized as de novo □ MCL, characterized by documentation of monoclonal B cells that have a chromosome translocation t(11;14)(q13;q32) and/or overexpress cyclin D1 □ iNHL o FL Grade 1, 2 or 3a o WM o CLL/SLL Note: Under Amendment 6 of this protocol, all active subjects will receive acalabrutinib monotherapy (100 mg BID). **Part 2** Part 2 consists of expansion groups of up to 12 subjects per histology provided the safety and efficacy results from Part 1 of the study indicate that further evaluation of the combination is warranted. The possible expansion groups for Part 2 could include adult subjects with the following disease types: □ Non-GCB DLBCL, characterized as de novo □ Germinal center B-cell subtype (GCB) DLBCL □ Richter's syndrome □ MCL, characterized by documentation of monoclonal B cells that have a chromosome translocation t(11;14)(q13;q32) and/or overexpress cyclin D1 □ iNHL o FL, Grade 1, 2, or 3a o WM o CLL/SLL □ Multiple myeloma (MM) □ B-cell acute lymphoblastic leukemia (B-ALL) Note: Under Amendment 4 of this protocol, enrollment in Part 2 is closed for all cohorts except the non-GCB DLBCL cohort. Note: Under Amendment 5 of this protocol, CCI [redacted] all subjects on combination therapy (acalabrutinib+ACP-319) discontinued ACP-319 and continued on monotherapy (acalabrutinib) at the subject's current dose at the investigator's discretion.

	Note: Under Amendment 6 of this protocol, all active subjects will receive acalabrutinib monotherapy (100 mg BID). Treatment with acalabrutinib (and previously ACP-319), in Part 1 and Part 2, may be continued until disease progression or an unacceptable drug-related toxicity occurs as defined in the protocol. Dose modification provisions are provided in the study protocol. Note: Temporary withholding of study drug for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. Refer to Section 3.12 for more information on assessing disease progression under these circumstances. All subjects who discontinue study treatment will have a safety follow-up visit 30 (+ 7) days after the last dose of study drug and will be followed every 3 months thereafter until disease progression or the start of alternative anticancer treatment. All subjects will have hematology, chemistry, and urinalysis safety panels performed at screening. Once dosing commences (Day 1), all subjects receiving acalabrutinib and ACP-319 combination therapy will be evaluated for safety, including serum chemistry and hematology, on Cycle 1 Days 1, 8, 15, 22, and 28, Cycle 2 Days 15 and 28, then monthly through Cycle 24, and every 3 months thereafter. ECGs will be obtained at screening, repeatedly during Cycle 1, at each study visit through Cycle 6, and at each study visit in Cycles 9 and 12. Pharmacokinetic testing will be done in Cycles 1 to 4. PD testing will be done in Cycles 1 and 2, and at the Treatment Termination (TT) visit. Radiologic tumor assessments will be done at screening and at the end of Cycle 2, Cycle 4, and Cycle 6; every 3 cycles (12 weeks) through Cycle 18, and then every 6 cycles thereafter, or more frequently at the investigator's discretion. Subjects showing clinical benefit and who are tolerating study treatment may remain on study until the end of study, defined as 36 months after the last subject is enrolled. Subjects who are still on treatment at the end of the study and deriving clinical benefit from acalabrutinib monotherapy may be eligible to enroll in a rollover or safety extension study of acalabrutinib monotherapy. Refer to Appendix 5 for a comprehensive list of study assessments and their timing (acalabrutinib monotherapy).
Definition of Dose-limiting Toxicity:	In Part 1, a DLT will be defined as the occurrence of any of the following ACP-319-related adverse events (AEs): 1. Any Grade ≥3 nonhematologic toxicity (except Grade 3 nausea, vomiting, or diarrhea that respond to supportive therapy) 2. Any of the following hematologic toxicities (for CLL): a. Grade 4 neutropenia lasting >7 days.

	b. Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia with bleeding, or any requirement for platelets transfusion. c. Grade 3 febrile neutropenia (temperature ≥38.5°C). d. Grade 4 anemia, unexplained by underlying disease. 3. Dosing delay due to toxicity for >28 consecutive days.
Study Objectives:	**Primary Objective:** □ To characterize the safety profile of acalabrutinib and ACP-319 in subjects with relapsed or refractory B-cell malignancies. **Secondary Objectives:** □ To document the extent of study drug exposure as determined by coadministration of acalabrutinib and ACP-319 □ To evaluate the pharmacodynamic effects of acalabrutinib and ACP-319 administration □ To evaluate the activity of acalabrutinib and ACP-319 as measured by response rate, duration of response, progression-free survival, and time-to-next treatment
Safety Parameters:	The safety of acalabrutinib and ACP-319 will be characterized by the type, frequency, severity, timing of onset, duration, and relationship to study drug(s) of any treatment-emergent AEs or abnormalities of laboratory tests; serious adverse events (SAEs); or AEs leading to discontinuation or dose reduction of study treatment.
Pharmacokinetic Parameters:	The plasma pharmacokinetics of acalabrutinib and ACP-319 and a metabolite (M20) of ACP-319 will be characterized using noncompartmental analysis. The following PK parameters will be calculated, whenever possible, from plasma concentrations of analytes: □ $AUC_{0\text{-last}}$ Area under the plasma concentration-time curve from time 0 to time last, calculated using trapezoidal summation, where “last” is the time of the last measurable concentration (C_t) □ $AUC_{0\text{-}12}$ Area under the plasma concentration-time curve from 0 to 12 hours, calculated using trapezoidal summation □ $AUC_{0\text{-inf}}$ Area under the plasma concentration-time curve from 0 to infinity, calculated using the formula: $AUC_{0\text{-inf}} = AUC_{0\text{-last}} + C_{last} / \lambda_z$, where λ_z is the apparent terminal elimination rate constant

	□ $AUC_{0\text{-}24calc}$ Area under the plasma concentration-time curve from 0 to 24 hours, calculated by doubling the value for $AUC_{0\text{-}12}$ □ C_{max} Maximum observed plasma concentration □ T_{max} Time of the maximum plasma concentration (obtained without interpolation) □ $t_{½}$ Terminal elimination half-life (whenever possible) □ λ_z Terminal elimination rate constant (whenever possible) □ CL/F Oral clearance □ Vz/F: Oral volume of distribution
Pharmacodynamic Parameters:	The occupancy of BTK by acalabrutinib will be measured in peripheral blood mononuclear cells (PBMCs) and bone marrow, when available, with the aid of a biotin-tagged acalabrutinib analogue probe. The effect of acalabrutinib and ACP-319 on biologic markers of B-cell function will also be evaluated.
Efficacy Parameters:	□ Overall response rate (ORR) □ Duration of response □ Progression-free survival □ Time-to-next treatment
Sample Size:	Part 1: Up to 18 subjects Part 2: Up to 108 subjects
Inclusion Criteria:	Eligible subjects will be considered for inclusion in this study if they meet **all** of the following criteria: **Part 1:** 1. Diagnosis of non-GCB DLBCL, MCL, or iNHL as documented by medical records and with histology based on criteria established by the World Health Organization (WHO). a) If the subject has DLBCL, it is characterized as de novo non-GCB DLBCL (Hans et al. 2004 or Choi et al. 2009). Note: primary mediastinal large B-cell lymphoma (PMBCL) is excluded from this protocol. b) If the subject has MCL, it is characterized by documentation of monoclonal B cells that have a chromosome translocation t(11;14)(q13;q32) and/or overexpress cyclin D1.

	c) If the subject has iNHL, the histology shows 1 of the following subtypes: i) FL Grade 1, 2, or 3a ii) WM iii) CLL/SLL 2. Prior treatment for lymphoid malignancy: a) If the subject has DLBCL, there is no curative option with conventional therapy and the prior treatment included ≥1 prior combination chemoimmunotherapy regimen (e.g., anthracycline based therapy with rituximab). b) If the subject has MCL or iNHL, the prior treatment comprised any of the following: i) ≥1 regimen containing an anti-CD20 antibody administered for ≥2 doses and/or ii) ≥1 regimen containing ≥1 cytotoxic agent (e.g., bendamustine, chlorambucil, cyclophosphamide, cytarabine, doxorubicin) administered for ≥2 cycles, and/or iii) ≥1 regimen containing yttrium^{90}-ibritumomab tiuxetan (Zevalin®) or iodine^{131}-tositumomab (Bexxar®). 3. Presence of radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (defined as the presence of a ≥2.0 cm lesion as measured in the longest dimension by computed tomography [CT] scan). Note: Not applicable to subjects with WM and MM. 4. Absolute neutrophil count (ANC) ≥1.5 x 10^9/L or platelet count ≥100 x 10^9/L unless due to disease involvement in the bone marrow. **All Parts:** 5. Men and women ≥18 years of age. 6. Documented active disease. 7. Eastern Cooperative Oncology Group (ECOG) performance status of ≤2. 8. Females must agree to use highly effective forms of contraception during the study and for 2 days after the last dose of acalabrutinib and 90 days after the last dose of APC-319, whichever is longer, if sexually active and able to bear children. Highly effective forms of contraception are defined in Section 3.11.4. 9. Males must agree to use highly effective forms of contraception while taking ACP-319 and for 90 days after their last dose of ACP-319, if sexually active and able to beget children. Males must also refrain from sperm

	donation during the study and for 90 days after the last dose of ACP-319. 10. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty. 11. Ability to understand the purpose and risks of the study and provide signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local patient privacy regulations). **Part 2 Additional disease entry criteria:** 12. DLBCL (GCB): Confirmed diagnosis of DLBCL with disease characterized as GCB subtype by immunohistochemistry (Hans et al. 2004 or Choi et al. 2009) and meeting the rest of the criteria as defined above, including characterization as de novo DLBCL. 13. Richter's syndrome: Confirmed diagnosis of previously treated CLL/SLL with previously untreated and biopsy-proven DLBCL due to Richter transformation and meeting the rest of the criteria as defined above. 14. MM: Confirmed diagnosis of MM, which has relapsed after, or been refractory to ≥1 prior therapy for MM and is progressing at the time of study entry and meeting the rest of the criteria as defined above. 15. B-ALL: Confirmed diagnosis of previously treated B-ALL and meeting the rest of the criteria as defined above.
Exclusion Criteria:	Subjects will be ineligible for this study if they meet **any** of the following criteria: **All Parts:** 1. Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject has been disease free for ≥2 years or which will not limit survival to <2 years. Note: These cases must be discussed with 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 and/or ACP-319, or put the study outcomes at undue risk. 3. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification. 4. Malabsorption syndrome, disease significantly affecting gastrointestinal (GI) function, resection of the stomach, extensive small bowel resection that is likely to affect

	absorption, symptomatic inflammatory bowel disease, partial or complete bowel obstruction, or gastric restrictions and bariatric surgery such as gastric bypass. 5. Central nervous system (CNS) involvement by lymphoma/leukemia. 6. Any therapeutic antibody within 4 weeks of first dose of study drug. 7. The time from the last dose of the most recent chemotherapy or experimental therapy to the first dose of study drug is <5 times the half-life of the previously administered agent(s). 8. Any prior therapy with BTK, PI3Kδ, or SYK inhibitors or BCL-2 inhibitors (e.g., venetoclax/ABT-199). Note: Prior treatment with reversible, noncovalent BTK inhibitors is not excluded on this protocol. 9. Ongoing immunosuppressive therapy, including systemic or enteric corticosteroids for treatment of lymphoid cancer or other conditions. Note: Subjects may use topical or inhaled corticosteroids or low-dose steroids (≤10 mg of prednisone or equivalent per day) as therapy for comorbid conditions. During study participation, subjects may also receive systemic or enteric corticosteroids as needed for treatment-emergent comorbid conditions. 10. Use of a strong inhibitor or inducer of cytochrome P450 (CYP)3A (see Appendix 3) within 7 days before dose of study drug or expected requirement for use of a CYP3A inhibitor or inducer during the first 28 days of administration of study drugs. 11. Remains not applicable for this amendment. 12. Known history of HIV, serologic status reflecting active hepatitis B or C infection, or any uncontrolled active systemic infection. a) Subjects who are hepatitis B core antibody (anti-HBc) positive and who are surface antigen negative will need to have a negative polymerase chain reaction (PCR) result before enrollment. Those who are hepatitis B surface antigen (HbsAg) positive or hepatitis B PCR positive will be excluded. b) Subjects who are hepatitis C antibody positive will need to have a negative PCR result before enrollment. Those who are hepatitis C PCR positive will be excluded. 13. Major surgery within 4 weeks before first dose of study drugs. Note: If a subject had major surgery, they must have recovered adequately from any toxicity and/or complications from the intervention before the first dose of study drug. 14. History of stroke or intracranial hemorrhage within 6 months before the first dose of study drugs. 15. Ongoing, drug-induced liver injury, alcoholic liver disease, nonalcoholic steatohepatitis, primary biliary cirrhosis, ongoing extrahepatic obstruction caused by cholelithiasis, cirrhosis of the liver, or portal hypertension.

	16. History of or ongoing drug-induced pneumonitis. 17. Part 2 only: ANC <0.5 x 10^9/L or platelet count <50 x 10^9/L unless due to disease involvement in the bone marrow. 18. 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]. 19. Significant screening ECG abnormalities including left bundle-branch block, second-degree atrioventricular (AV) block type II, third-degree AV block, Grade ≥2 bradycardia, and QTc >480 msec. 20. Breastfeeding or pregnant. 21. Concurrent participation in another therapeutic clinical trial. 22. History of bleeding diathesis (e.g., hemophilia or von Willebrand disease). 23. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon) within 7 days of first dose of study drug. 24. Requires treatment with proton-pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). Subjects receiving proton-pump inhibitors who switch to H2-receptor antagonists or antacids are eligible for enrollment to this study. 25. Total bilirubin >1.5 x upper limit of normal (ULN), or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 x ULN. 26. Serum amylase >1.5 x ULN or serum lipase >1.5 x ULN. 27. Presence of a GI ulcer diagnosed by endoscopy within 3 months before screening. 28. Concomitant use of medicines known to cause QT prolongation or Torsades de pointes within 7 days of starting study drug (see Appendix 2) 29. Active cytomegalovirus (CMV) infection (positive CMV immunoglobulin (Ig) M and/or positive PCR result).
Dosage Form and Strength:	Acalabrutinib will be provided in white, high-density polyethylene bottles. ACP-319 will be provided in high-density polyethylene bottles.
Dose Regimen/Route of Administration:	Both drugs are intended to be administered orally BID with 8 ounces (approximately 240 mL) of water. Subjects receiving acalabrutinib and ACP-319 combination therapy should be instructed to take each dose of both study drugs at the same time on an empty stomach, defined as no food 2 hours before and 1 hour after dosing. Subjects receiving acalabrutinib monotherapy are not required to fast before and after acalabrutinib administration. The capsules should be swallowed intact. Subjects should not attempt to open the capsules or dissolve them in water. Doses should be taken 12 hours (± 60 minutes) apart.

	Regimens: **Part 1:** Cohort 1: Acalabrutinib 100 mg BID + ACP-319 25 mg BID continuously Cohort 2: Acalabrutinib 100 mg BID + ACP-319 50 mg BID continuously Cohort 3: Acalabrutinib 100 mg BID + ACP-319 100 mg BID continuously **Part 2:** Acalabrutinib 100 mg BID + ACP-319 50 mg BID continuously Note: Under Amendment 6 of this protocol, all active subjects will receive acalabrutinib monotherapy (100 mg BID).
Concomitant Medications:	The effect of agents that reduce gastric acidity (antacids or proton-pump inhibitors) on acalabrutinib absorption was evaluated in a healthy volunteer study (ACE-HV-004). Results from this study indicate that subjects should avoid the use of calcium carbonate-containing drugs or supplements for a period of at least 2 hours before and at least 2 hours after taking acalabrutinib. Use of omeprazole, 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 GI 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. The concomitant use of strong inhibitors/inducers of CYP3A with acalabrutinib 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. Detailed information on concomitant administration of drugs that inhibit or induce CYP3A is provided in Section 3.11.3 and Appendix 3.
Statistics:	Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions and confidence intervals [CIs] for discrete variables) will be used to summarize data as appropriate. As appropriate, analyses will be performed by dosing cohort, cancer type, or overall. Depending on dose escalation into subsequent cohorts and

	potential expansion cohorts, up to 108 evaluable subjects will be enrolled in this study. In Part 1 (dose-escalation portion), enrollment of 6 subjects per cohort of the study limits the total cohort size consistent with the expected safety profiles of the study drugs but includes sufficient subjects per cohort to explore dose-dependent effects on PD biomarkers of BTK and PI3Kδ inhibition. The study employs the standard National Cancer Institute definition of MTD (starting dose associated with Cycle 1 DLT in <33.3% of subjects). In Part 2 (expansion groups), enrollment of up to 12 subjects per histology offers the opportunity to determine if there is sufficient antitumor activity to warrant further development in the selected tumor types.

1.0 BACKGROUND INFORMATION

1.1 A CASE FOR TARGETED COMBINATION THERAPY IN B-CELL MALIGNANCIES

Through decades of clinical experience, the use of multidrug regimens has been shown to produce higher complete remission (CR) rates and more durable responses, resulting in improved survival in most oncology indications. However, these benefits are often outweighed with the increased toxicity associated with multidrug regimens. This high risk-benefit ratio limits the use of many effective multidrug regimens in elderly patients or patients with comorbid conditions.

The advent of highly selective, targeted agents such as Bruton tyrosine kinase (BTK) and phosphatidylinositol 3-kinase p110-delta (PI3Kδ) inhibitors has changed the risk-benefit paradigm traditionally associated with cytotoxic chemotherapy regimens. Small molecule inhibitors of BTK and PI3Kδ produce high overall response rates (ORRs) with few drug-related toxicities in patients with B-cell malignancies. For example, ibrutinib, a first-generation oral, small molecule BTK inhibitor, has been approved for the treatment for chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL; IMBRUVICA [prescribing information] 2014). In addition, ibrutinib has shown clinical efficacy in other non-Hodgkin lymphoma (NHL) histologies, including follicular lymphoma (FL; Advani et al. 2012), diffuse large B-cell lymphoma (DLBCL; De Vos et al. 2013), and in Waldenström macroglobulinemia (WM; Treon et al. 2013). Preliminary data suggests that patients with multiple myeloma (MM) with high BTK activity, as evidenced by phosphorylated BTK, may be particularly responsive to BTK inhibitor therapy (Liu et al. 2014). In preclinical studies, BTK inhibition significantly reduced MM cell growth and tumor-induced osteolysis in a murine model (Tai et al. 2012). Idelalisib, a small molecule PI3Kδ inhibitor, was recently approved for treatment of relapsed CLL in combination with rituximab and third-line treatment of FL and small lymphocytic lymphoma (SLL; ZYDELIG [prescribing information] 2014). Idelalisib has shown an ORR of 57% (51% PR and 6% CR) in a Phase 2 study in subjects with previously treated indolent NHL (iNHL; Gopal et al. 2014). Despite these significant advances, the investigation of additional treatment regimens is essential to improve outcomes in B-cell malignances. A low proportion of patients achieve CR when treated with single-agent BTK or PI3Kδ inhibitors compared with conventional chemotherapy or chemoimmunotherapy regimens. Moreover, the median duration of response can be brief (<12 months) in aggressive histologies.

The question remains as to whether "targeted combination" therapy can produce more durable responses and potentially more CRs than single agents without an associated increase in toxicity. Certainly, recent clinical data from a Phase 1 and 2 trial of combined treatment with dabrafenib, a selective BRAF inhibitor, and trametinib, a selective mitogen-activated protein kinase (MAPK) kinase (MEK) inhibitor in melanoma suggests this promise may be fulfilled. The combination, when compared with dabrafenib monotherapy, produced statistically significant greater progression-free survival, ORR, and median duration of response without an increase in toxicities (Flaherty et al. 2012).

Preclinical models have demonstrated the potential for synergy between the PI3Kδ and BTK pathways. PI3Kδ is thought to activate BTK; however, data from PI3Kδ$^{-/-}$ mice show that activation of BTK through the B-cell receptor (BCR) does not require PI3Kδ (Suzuki et al. 2003). Mice deficient in PI3Kδ and BTK have more profound B-cell defects than either single-mutant mouse strain. In addition to mediating B-cell activation, PI3Kδ and BTK independently down-regulate the expression and function of forkhead box protein O1 (FOXO1) through various mechanisms (Hinman et al. 2007). FOXO1 is a transcription factor for pro-apoptotic and antimitogenic genes, and PI3Kδ and BTK are thought to mediate BCR-induced proliferation and survival in part by down-regulating FOXO1. In addition, nonclinical and clinical data have demonstrated that BTK inhibition alters B-cell recirculation patterns, removing lymphoma cells from protective microenvironment niches and potentially removing them from proximal growth signals (Smith et al. 2015a). Inhibition of BTK and PI3Kδ may also have direct effects on the nonmalignant cells within the tumor microenvironment (López-Herrera et al. 2014). Thus, dual inhibition of BTK and PI3Kδ in patients with B-cell malignancies may ultimately increase the proportion of patients with CRs by promoting apoptosis in malignant B cells through multiple mechanisms. Dual pathway inhibition may increase response durations, due to reduced opportunity for mechanistic resistance (i.e., resistance-conferring mutations would be required in both pathways). Anecdotal reports emerging from clinical studies of ibrutinib and idelalisib suggest that some patients who fail to respond to one kinase inhibitor can subsequently respond well to the other. These early observations may indicate a lack of cross resistance for these signaling pathways.

Strong clinical and mechanistic rationale exist to expect increased efficacy with dual inhibition of BTK and PI3Kδ. Based on known pathway-related side effects, improved activity may be achievable without a worsening toxicity profile. If so, this dual inhibition approach may improve outcomes for difficult-to-treat patients, including frail or elderly patients and individuals with comorbidities. If activity is sufficiently high, dual inhibition of

BTK and PI3Kδ may be an attractive approach to avoid or delay use of cytotoxic chemotherapy regimens in treatment-naive patients with B-cell malignancies.

Acerta Pharma is developing a potent, highly selective covalent BTK inhibitor, acalabrutinib (also known as ACP-196 and CALQUENCE®). 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 line of therapy, CLL, and small lymphocytic lymphoma (SLL). CCI

This proof-of-concept study will assess the clinical potential of a dual inhibition approach by evaluating the safety, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy acalabrutinib and ACP-319 in B-cell malignancies.

Summaries of preclinical studies for acalabrutinib and ACP-319 are provided below. For more detailed information please refer to the Investigator Brochures for acalabrutinib and ACP-319 (AMG 319).

1.2 CHEMISTRY – ACALABRUTINIB AND ACP-319

Acalabrutinib and ACP-319 are small molecule kinase inhibitors. Acalabrutinib is a covalent inhibitor of BTK and ACP-319 is a reversible inhibitor of PI3Kδ. Both molecules are orally administered and suitable for formulating in capsules.

1.3 EFFICACY PHARMACOLOGY

1.3.1 In Vitro Assays

The in vitro effects of acalabrutinib on cell viability were investigated using a panel of 10 cell lines representing different B-cell lymphoma histologies, including DLBCL (6 cell lines), MCL (3 cell lines), and Burkitts lymphoma (BL; 1 cell line). Sensitivity to acalabrutinib was defined as growth inhibition with a concentration of a drug that gives half-maximal response (EC_{50}) value <500 nM. Four DLBCL and 2 MCL lines were classified as sensitive cells (Table 1-1). Of the lymphoma lines evaluated, DLBCL cells displayed the highest degree of sensitivity with EC_{50} values <200 nM. Growth of the BL line was modestly inhibited with an EC_{50} value of 1.5 µM.

Table 1-1. Antiproliferative Activity of Acalabrutinib in Cell Lines Derived from Various Hematologic Malignancies

Cell Line	Indication	EC_{50} nM
TMD8	DLBCL (ABC)	57
HBL1	DLBCL (ABC)	68
SU-DHL-2	DLBCL (ABC)	165
DOHH	DLBCL (GCB)	3,500
SU-DHL-4	DLBCL (GCB)	120
SU-DHL-6	DLBCL (GCB)	> 5,000
JEKO	MCL	439
REC-1	MCL	439
MINO	MCL	> 5,000
Daudi	Burkitts	1,500

Abbreviations: ABC DLBCL = activated B-cell subtype of diffuse large B-cell lymphoma; EC_{50} = concentration that gives half-maximal response; GCB DLBCL = germinal-center B-cell subtype of diffuse large B-cell lymphoma; MCL = mantle cell lymphoma. Note: Cellular EC_{50} determined using Cell Titer Glow™.

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1.3.3 Spontaneous Canine B-Cell Lymphoma

Spontaneous canine B-cell lymphoma shares many characteristics with human NHL, including diagnostic classifications and response to BTK inhibition (Honigberg et al. 2010). The life expectancy in untreated animals with aggressive disease is ~6 weeks, thus enabling rapid assessment of drug efficacy (Vail et al. 2004). Acalabrutinib was evaluated in a dose-escalation study in canine spontaneous B-cell lymphoma (ACE-NC-001, Harrington et al. 2016). Twenty dogs were enrolled in the clinical trial and treated with acalabrutinib at dosages of 2.5 to 20 mg/kg every 12 or 24 hours. Acalabrutinib was generally well tolerated, with adverse events (AEs) 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 et al. 2010), ORR was 25% (5/20) with a median progression free survival 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 canines with B-cell lymphoma and support the use of canine lymphoma as a relevant model for human NHL. These findings are similar to the clinical responses (i.e., 1 dog with PR out of 5 dogs treated with suspected or confirmed DLBCL) observed with ibrutinib in dogs with spontaneous B-cell lymphoma (Honigberg at al. 2010).

Preliminary results assessing BTK occupancy in dogs using a biotin-tagged analogue of acalabrutinib show near complete BTK occupancy over 24 hours with twice daily (BID) versus once daily (QD) dosing in canine tumor tissue (Table 1-3). In addition, reversal of disease progression was observed in 3 dogs when switched from acalabrutinib QD to

BID dosing with a longer duration of response (Gardner et al. 2014)—suggesting BID dosing may be more efficacious in aggressive disease.

Table 1-3. Assessment of Acalabrutinib Active-site Occupancy in Fine Needle Aspirates of Canine Lymph Node Tumors (N=4)

Timing	Dog Identification and Acalabrutinib Dosing Regimen			
	DL-10	DL-12	DL-14	DL-16
	5 mg/kg QD	10 mg/kg BID	20 mg/kg QD	20 mg/kg QD
	BTK Occupancy (% versus predose)			
Day 1 (3 hours after morning dose)	98%	99%	98%	99%
Day 7 (before morning dose)	80%	98%	77%	93%

Abbreviations: BID = twice daily; BTK = Bruton tyrosine kinase; ND = not determined; QD = once daily.

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Taken together, the results from study ACE-NC-001 demonstrate biologic and clinical activity in a difficult-to-treat model of aggressive lymphoma.

1.4 PHARMACOLOGY – ACALABRUTINIB

1.4.1 Primary and Secondary Pharmacology

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 half-maximal inhibitory concentration (IC_{50}) of 2.7 µM, suggesting a low clinical risk of off-target effects. Acalabrutinib at 10 µM showed no inhibition of in vitro epidermal growth factor receptor (EGFR) phosphorylation in an A431 human epidermoid cancer cell line whereas ibrutinib had an IC_{50} of 66 nM.

1.4.2 Safety Pharmacology

In vitro and in vivo safety pharmacology studies with acalabrutinib have demonstrated a favorable nonclinical safety profile. 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. Acalabrutinib at 0.9 µM (nominally 1 µM) was determined to be a no effect level. This concentration is 53 times higher than the clinical unbound C_{max} at steady state for a 100-mg dose (17 nM). No acalabrutinib-related effects (body temperature, cardiovascular, or ECG parameters) were observed in the dog cardiovascular safety study at 30 mg/kg, the highest dose administered. The total exposure at 30 mg/kg/day was at least 14-fold greater than the clinical steady state exposure at the clinical dose of 100 mg BID. Healthy subjects administered acalabrutinib in therapeutic (100 mg) or supratherapeutic (400 mg) doses (HV-005) demonstrated no compound induced changes in mean systolic or diastolic arterial blood pressure, heart rate, and QTc during a 24-hour recording period. Based on the in vitro and in vivo cardiovascular data, there is a low clinical risk that acalabrutinib would induce clinical QT prolongation as predicted by this assay.

No neurobehavioral effects or significant changes in respiratory parameters were noted for acalabrutinib following a single oral administration up to 300 mg/kg (the highest dose level) in a functional observation batter in rats.

The results suggest that acalabrutinib is unlikely to cause serious off-target effects or adverse effects on critical organ systems.

1.5 SAFETY PHARMACOLOGY – ACP-319

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1.6 SAFETY PHARMACOLOGY – ACALABRUTINIB AND ACP-319

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1.7 DRUG-DRUG INTERACTION POTENTIAL – ACALABRUTINIB

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

Please refer to Section 3.11.3 for guidance on drugs that may cause drug-drug interactions.

1.8 DRUG-DRUG INTERACTION POTENTIAL – ACP-319

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1.9 DRUG-DRUG INTERACTION POTENTIAL – ACALABRUTINIB AND ACP-319

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Acalabrutinib was not a strong inhibitor of CYP3A (IC_{50} of 57 µM) or AO (IC_{50} >100 µM)

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1.10 IN VIVO GENERAL TOXICOLOGY – ACALABRUTINIB

Refer to the acalabrutinib Investigator Brochure for the description and discussion of general toxicology findings.

1.11 IN VIVO GENERAL TOXICOLOGY – ACP-319

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1.12 IN VIVO GENERAL TOXICOLOGY – ACALABRUTINIB AND ACP-319

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1.13 CLINICAL EXPERIENCE

1.13.1 Acalabrutinib Studies

For more detailed information on the clinical experience for acalabrutinib please refer to the Investigator Brochure. This section briefly summarizes data from 3 studies of acalabrutinib: ACE-HV-001, ACE-HV-004, and ACE-CL-001.

1.13.1.1 Pharmacokinetics and Pharmacodynamics of Acalabrutinib in Healthy Volunteers

ACE-HV-001 was a PK/PD, dose-ranging, food-effect, and drug-drug interaction study evaluating acalabrutinib BID and QD dosing for 1 or 2 days in healthy volunteers. This study evaluated the PK/PD of acalabrutinib at various dose levels and regimens. The starting dose for acalabrutinib was 2.5 mg BID. This study has been completed and no adverse laboratory, vital signs, or ECG findings were observed (2.5 to 50 mg BID; 50 to 100 mg QD). Three AEs related to acalabrutinib were reported. Each AE was Grade 1 and resolved without treatment. The AEs were constipation (2.5 mg BID), feeling cold (75 mg QD), and somnolence (75 mg QD).

Median acalabrutinib plasma 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} values decreased to 27.3% of the values observed in the fasted state. In contrast, the relative exposure of acalabrutinib (AUC) remained mostly unchanged in both states.

The effect of coadministration of a potent CYP3A4 inhibitor, itraconazole, on the plasma levels of acalabrutinib was also evaluated. The mean plasma acalabrutinib C_{max} values increased 3.7-fold in the presence of itraconazole. The mean plasma $AUC_{0\text{-last}}$, $AUC_{0\text{-}24}$, and AUC from 0 to infinity ($AUC_{0\text{-inf}}$) values also increased between 4.9- to 5.1-fold in the

presence of itraconazole. Mean oral clearance (CL/F) and oral volume of distribution (Vz/F) values decreased in the presence of itraconazole.

ACE-HV-004 was a 3-part, 2-period drug interaction study in 72 healthy volunteers, which evaluated the pharmacokinetics of a single dose of acalabrutinib (100 mg) administered alone or coadministered with a single oral dose of calcium carbonate (1 g), with omeprazole (40 mg) on the fifth consecutive day of omeprazole dosing, or with rifampin (600 mg) on the first and ninth days of 9 consecutive days of rifampin dosing. Acalabrutinib administration was well tolerated; further details are provided in the acalabrutinib Investigator Brochure. Coadministration of the gastric pH modifiers, calcium carbonate or omeprazole, decreased mean C_{max} to 25% and 21% and AUC to 47% and 43%, respectively, of values obtained with acalabrutinib dosed alone. Rifampin dosed at 600 mg QD for 9 days decreased AUC to 23% of values obtained with acalabrutinib dosed alone.

1.13.1.2 Clinical Experience of Acalabrutinib in CLL

As of 01 October 2015, acalabrutinib has been administered to >800 participants in clinical studies, including subjects with hematologic malignancies, solid tumors, or rheumatoid arthritis, and participants who are healthy volunteers or with mild to moderate hepatic impairment. No serious adverse events (SAEs) have been reported in the hepatic impairment study or in the healthy volunteer studies. For more detailed information on the clinical experience for acalabrutinib, please refer to the Investigator Brochure.

This section briefly summarizes data from **ACE-CL-001** (NCT02029443), an ongoing nonrandomized, sequential group, dose-escalation Phase 1/2 study in subjects with relapsed/refractory or previously untreated CLL, Richter's syndrome, or prolymphocytic leukemia.

As of 01 October 2015, 60 subjects with relapsed CLL have been evaluated for tumor response based on modified International Working Group response criteria (Hallek et al. 2008) as recently updated (Cheson et al. 2012) to include PR with treatment-induced lymphocytosis (PRL). With a median follow-up of 14.3 months, an ORR of 95% has been observed (Byrd et al. 2016). Few subjects have had disease progression and no Richter's transformation has been observed in these subjects.

1.13.2 ACP-319 First-in-Human Study

ACP-319 monotherapy has been evaluated in a first-in-human trial (FIH), dose-escalation study (25 to 400 mg QD) in subjects with relapsed or refractory lymphoid malignancies (Amgen Study #20101262/NCT01300026). Key eligibility criteria included requirements that subjects be ≥18 years old, have an Eastern Cooperative Oncology Group (ECOG) performance status ≤2, and demonstrate adequate organ function. ACP-319 was administered until disease progression or unacceptable toxicity. DLTs were evaluated during the first 28 days of ACP-319 administration.

Enrollment in this study is complete. Because the protocol allowed subjects to continue with ACP-319 treatment until disease progression or intolerable AE, the study is still ongoing. The results from the most recent clinical database review, 31 October 2013, are provided below.

Twenty-eight subjects received ACP-319 (6 at 25 mg; 3 at 50 mg, 100 mg, 200 mg, and 300 mg; and 10 at 400 mg; all doses were given QD). The most common AEs experienced by subjects during the initial assigned dose levels (in at least 25% of subjects) were cough 13 (46%), diarrhea 13 (46%), fatigue 10 (36%), pyrexia 10 (36%), nausea 9 (32%), and anemia 7 (25%). SAEs that occurred in >1 subject each were febrile neutropenia, disease progression, device-related infection, lung infection, and pneumonia (each 2 subjects [7%]), and pyrexia (3 subjects [11%]). SAEs that were assessed by the investigator to be treatment-related (including those occurring after intrasubject dose escalation) occurred in 6 subjects: hemolysis, hypoxia, and pneumonia; hemolysis; pyrexia, *Clostridium difficile* colitis, and infection; abdominal pain and decreased appetite; colitis, neutropenia, and febrile neutropenia; and exfoliative dermatitis.

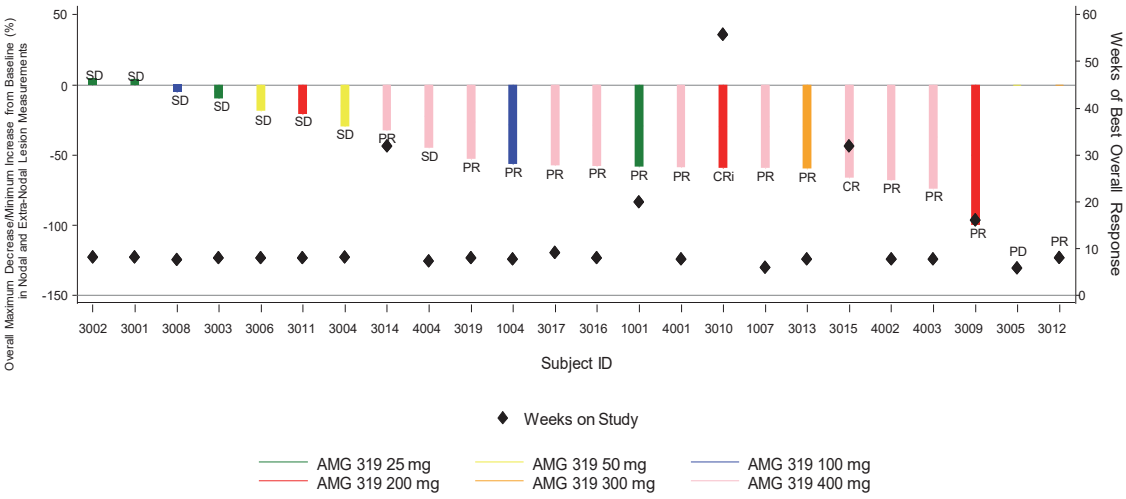
One subject experienced a DLT (Grade 3 hemolysis). This subject had received rasburicase on the same day as ACP-319; rasburicase is associated with hemolysis and methemoglobinemia and includes a “black box” warning for these events (ELITEK [prescribing information] 2011). One subject died due to a thromboembolic event that was assessed by the investigator as unrelated to ACP-319, and 1 subject died due to disease progression. A trend towards QTcF prolongation was noted in the 400-mg cohort; however, no QTcF >500 msec or increase >60 msec from baseline has been observed.

PK data are available from 26 subjects who remained on treatment through Day 29 after receiving daily oral ACP-319 doses of 25 to 400 mg. Median estimates of T_{max} ranged

from 0.9 to 2.0 hour and estimates of mean $t_{1/2}$ ranged from 3.0 to 3.9 hour. Mean estimates of C_{max} and AUC_{0-24} were 6.15 µg/mL and 30.2 µg•h/mL, respectively, after 29 days at the 400-mg dose level. ACP-319 plasma exposure generally increased with increasing dose and tended to plateau across the 300- and 400-mg dose levels. Mean ACP-319 accumulation ratios on Day 29 ranged from 0.924 to 1.87.

Consistent reductions in lymphadenopathy were observed at all doses by CT scans (Figure 1-2). Responses were present in all cytogenetic subtypes. At the 200- to 400-mg dose levels, 13 of 15 subjects with CLL remained on study after a median follow-up of 30 weeks (range 14 to 65 weeks). In summary, ACP-319 was well tolerated over periods extending to >18 months and antitumor activity was observed across all dose levels in subjects with CLL.

Figure 1-2. The Maximum Percentage Improvement of the Overall Sum of Cross Product in Nodal and Extra-Nodal Lesions from Radiological Assessment for CLL Subjects Safety Analysis Set



Data collected after the intra-subject dose escalation are not included in this graph.
CR=Complete Remission, CRi=CR with incomplete Marrow Recovery, PR=Partial Remissione, SD=Stable Disease, PD=Progressive Disease, NA=Not Applicable, NE=Non-Evaluable
Reporting Period: Inception to 31OCT2013

Program: /userdata/earlydev/AMG319/20101262/analysis/primary_analysis/figures/program/f-eff-max-per-impr-overall-nod-radio-cll-eff.sas
Output: f14-04-001-002-eff-max-per-impr-overall-nod-radio-cll-eff-l.rtf (Date Generated: 30JAN14 06:58) Source Data: crt.trcrir, crt.subjlvl

1.14 BENEFIT/RISK

Acalabrutinib is a potent, orally administered small molecule inhibitor of BTK. As described in Section 1.13.1, a PK/PD study has been completed with acalabrutinib in healthy volunteers (ACE-HV-001). The safety results showed no safety risk was identified in healthy subjects receiving 1 or 2 days of acalabrutinib ≤100 mg. In the Phase 1/2 study of acalabrutinib in subjects with CLL, an ORR of 95% has been observed with a median follow-up of 14.3 months. 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 CLL including those with 17p del. 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. For more detailed information on the clinical experience for acalabrutinib please refer to the Investigator Brochure.

ACP-319 has been evaluated in a FIH, dose-escalation study (25 to 400 mg QD) in subjects with relapsed or refractory lymphoid malignancies, as described in Section 1.13.2. The drug was generally well tolerated at all dose levels and no MTD was established over this dose range. In subjects with CLL, the drug showed anticancer activity across all tested doses.

Strong clinical and mechanistic rationale exist to expect increased efficacy with dual inhibition of BTK and PI3Kδ (see Section 1.1). Based on known pathway-related side effects as well as nonclinical safety pharmacology (Section 1.6) and toxicology (Section 1.12) studies of the combination of acalabrutinib and ACP-319, improved activity may be achievable without a worsening toxicity profile.

2.0 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

- To characterize the safety profile of acalabrutinib and ACP-319 in subjects with relapsed or refractory B-cell malignancies

2.2 SECONDARY OBJECTIVES

- To document the extent of study drug exposure as determined by coadministration of acalabrutinib and ACP-319
- To evaluate the PD effects of acalabrutinib and ACP-319 administration
- To evaluate the activity of acalabrutinib and ACP-319 as measured by response rate, duration of response, progression-free survival, and time-to-next treatment

3.0 STUDY DESIGN

This study is a multicenter, open-label, nonrandomized, sequential group, dose-escalation study to be conducted at approximately 30 sites. The study is divided into 2 parts: Part 1 of the study is the dose-escalation portion and Part 2 allows for possible expansion groups (Figure 3-1).

A cycle is defined as a period of 28 days.

Part 1

In each dose-escalation cohort, subjects will take acalabrutinib (and previously ACP-319) BID at approximately 12-hour intervals. The acalabrutinib dose will be fixed at 100 mg BID. The ACP-319 dose will be escalated as follows:

- Cohort 1: Acalabrutinib 100 mg BID + ACP-319 25 mg BID continuously
- Cohort 2: Acalabrutinib 100 mg BID + ACP-319 50 mg BID continuously
- Cohort 3: Acalabrutinib 100 mg BID + ACP-319 100 mg BID continuously

Each dosing cohort will be enrolled sequentially with 6 subjects per cohort. If ≤1 dose-limiting toxicity (DLT) (see below for definition) is observed in the cohort during Cycle 1, escalation to the next cohort will proceed. If ≥2 DLTs are observed during Cycle 1, dosing at that dose and higher will be suspended and the maximum tolerated dose (MTD) will be established as the previous cohort. The MTD is defined as the highest daily dose for which fewer than 33% of the subjects experience a DLT during Cycle 1. Escalation will end with Cohort 3 or sooner if the MTD is reached in an earlier cohort.

Part 1 of the study will include adult subjects with the following disease types:

- Non-germinal center B-cell subtype (non-GCB) diffuse large B-cell lymphoma (DLBCL), characterized as de novo
- MCL, characterized by documentation of monoclonal B cells that have a chromosome translocation t(11;14)(q13;q32) and/or overexpress cyclin D1
- iNHL
    - FL Grade 1, 2 or 3a
    - WM
    - CLL/SLL

Note: Under Amendment 6 of this protocol, all active subjects will receive acalabrutinib monotherapy (100 mg BID).

Part 2

Part 2 consists of expansion groups of up to 12 subjects per histology provided the safety and efficacy results from Part 1 of the study indicate that further evaluation of the combination is warranted. The possible expansion groups for Part 2 could include adult subjects with the following disease types:

- Non-GCB DLBCL, characterized as de novo

- Germinal center B-cell subtype (GCB) DLBCL
- Richter's syndrome
- MCL, characterized by documentation of monoclonal B cells that have a chromosome translocation t(11;14)(q13;q32) and/or overexpress cyclin D1
- iNHL
    - FL, Grade 1, 2, or 3a
    - WM
    - CLL/SLL
- Multiple myeloma (MM)
- B-cell acute lymphoblastic leukemia (B-ALL)

Note: Under Amendment 4 of this protocol, enrollment in Part 2 is closed for all cohorts except the non-GCB DLBCL cohort.

Note: Under Amendment 6 of this protocol, all active subjects will receive acalabrutinib monotherapy (100 mg BID).

Treatment with acalabrutinib (and previously ACP-319), in Part 1 and Part 2, may be continued until disease progression or an unacceptable drug-related toxicity occurs as defined in the protocol. Dose modification provisions are provided in the study protocol. Note: Temporary withholding of study drug for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. Refer to Section 3.12 for more information on assessing disease progression under these circumstances. All subjects who discontinue study treatment will have a safety follow-up (SFU) visit 30 (+ 7) days after the last dose of study drug and will be followed every 3 months thereafter until disease progression or the start of alternative anticancer treatment.

All subjects will have hematology, chemistry, and urinalysis safety panels performed at screening. Once dosing commences (Day 1), all subjects receiving acalabrutinib (and previously ACP-319) combination therapy will be evaluated for safety, including serum chemistry and hematology, on Cycle 1 Days 1, 8, 15, 22, and 28, Cycle 2 Days 15 and 28, then monthly through Cycle 24, and every 3 months thereafter. ECGs will be obtained at screening, repeatedly during Cycle 1, at each study visit through Cycle 6, and at each study visit in Cycles 9 and 12. PK testing will be done in Cycles 1 to 4. PD testing will be done in Cycles 1 and 2, and at the treatment termination (TT) visit. Radiologic tumor assessments will be done at screening and at the end of Cycle 2, Cycle 4, and Cycle 6; every 3 cycles (12 weeks) through Cycle 18, and then every 6 cycles thereafter, or more frequently at the investigator's discretion.

Refer to Appendix 5 for a comprehensive list of study assessments and their timing (acalabrutinib monotherapy).

Subjects showing clinical benefit and who are tolerating study treatment may remain on study until the end of study, defined as 36 months after the last subject is enrolled. Subjects who are still on treatment at the end of the study and deriving clinical benefit from acalabrutinib monotherapy may be eligible to enroll in a rollover or safety extension study of acalabrutinib monotherapy.

Subjects who are still on treatment at the end of the study and deriving clinical benefit from acalabrutinib treatment may continue treatment. At the time of the final data cutoff and database closure, subjects who remain in this study may be transitioned to a separate rollover study or remain within this study for continued access to study drug. Once all active subjects are eligible to continue to receive acalabrutinib and after database closure, this study would be considered closed. There will be no further data collection other than reporting of SAEs per Section 6.3. Access within this study will enable continued treatment with visit assessments per standard of care, whereas the separate rollover study will enable treatment continuation with visit assessments and data collection per the rollover study protocol.

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

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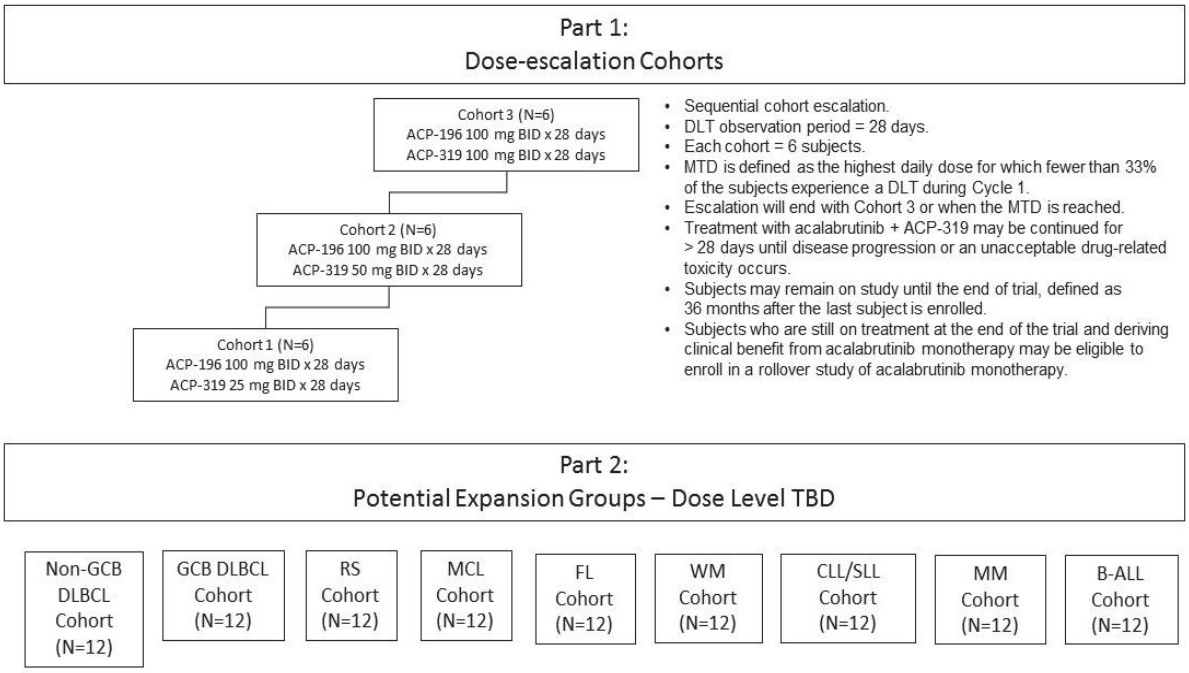
, effective 30 September 2018, all subjects on combination therapy (acalabrutinib+ACP-319) discontinued ACP-319 and continued on monotherapy (acalabrutinib) at the subject's current dose at the investigator's discretion.

Under Amendment 6, all ongoing subjects continued on acalabrutinib monotherapy.

Figure 3-1. Study Schema



Abbreviations: B-ALL = B-cell acute lymphoblastic leukemia; BID = twice daily; CLL/SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma; DLT = dose-limiting toxicity; FL= follicular lymphoma; GCB = germinal center B-cell diffuse large B-cell lymphoma; MM = multiple myeloma; MTD = maximum tolerated dose; non-GCB DLBCL = non-germinal center B-cell diffuse large B-cell lymphoma; RS = Richter's syndrome; TBD = to be determined; WM = Waldenström macroglobulinemia.
Note: Under Amendment 3 of this protocol, subjects with CLL/SLL in Parts 1 and 2 will receive acalabrutinib monotherapy (100 mg BID).
Note: Under Amendment 4 of this protocol, enrollment in Part 2 is closed for all cohorts except the non-GCB DLBCL cohort.
Note: Under Amendment 5 of this protocol, subjects still deriving clinical benefit from monotherapy may be eligible to enroll in a rollover or safety extension study of acalabrutinib monotherapy.
Note: Under Amendment 6 of this protocol, all active subjects will receive acalabrutinib monotherapy (100 mg BID).

3.1 STUDY PARAMETERS

3.1.1 Safety Parameters

The safety of acalabrutinib and ACP-319 will be characterized by the type, frequency, severity, timing of onset, duration, and relationship to study drug(s) of any treatment-emergent AEs or abnormalities of laboratory tests; SAEs; or AEs leading to discontinuation or dose reduction of study treatment.

For consistency of interpretation, AEs and laboratory results will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and the severity of AEs will be graded using the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 or higher. Standard definitions for seriousness will be applied (see Section 6.2).

3.1.2 Pharmacokinetic and Pharmacodynamic Parameters

Standard PK parameters for acalabrutinib in plasma will be evaluated in this study. A full description of the PK parameters is provided in Section 5.4.5.

The occupancy of BTK by acalabrutinib will be measured in peripheral blood mononuclear cells (PBMCs) and bone marrow, when available, with the aid of a biotin-tagged acalabrutinib analogue probe. The effect of acalabrutinib and ACP-319 on biologic markers of B-cell function will also be evaluated.

3.1.3 Efficacy Parameters

Standardized response and progression criteria have been established for B-cell malignancies, including WM (Bladé et al. 1998; Durie et al. 2006; Hallek et al. 2008; Owen et al. 2013; and Cheson et al. 2014); assessments of acalabrutinib and ACP-319 efficacy in this study will be based on these criteria. Efficacy endpoints will include:

- Overall response rate (ORR)
- Duration of response
- Progression-free survival
- Time-to-next treatment

3.2 RATIONALE FOR STUDY DESIGN AND DOSING REGIMEN

Refer to Protocol Amendment 5.0 for rationale for study design and dosing regimen.

3.3 SELECTION OF STUDY POPULATION

3.3.1 Inclusion Criteria

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

Part 1:

1. Diagnosis of non-GCB DLBCL, MCL, or iNHL as documented by medical records and with histology based on criteria established by the World Health Organization (WHO).
   a) If the subject has DLBCL, it is characterized as de novo non-GCB DLBCL (Hans et al. 2004 or Choi et al. 2009). Note: primary mediastinal large B-cell lymphoma (PMBCL) is excluded from this protocol.

b) If the subject has MCL, it is characterized by documentation of monoclonal B cells that have a chromosome translocation t(11;14)(q13;q32) and/or overexpress cyclin D1.

c) If the subject has iNHL, the histology shows 1 of the following subtypes:

i) FL Grade 1, 2, or 3a

ii) WM

iii) CLL/SLL

2. Prior treatment for lymphoid malignancy:

a) If the subject has DLBCL, there is no curative option with conventional therapy and the prior treatment included ≥1 prior combination chemoimmunotherapy regimen (e.g., anthracycline based therapy with rituximab).

b) If the subject has MCL or iNHL, the prior treatment comprised any of the following:

i) ≥1 regimen containing an anti-CD20 antibody administered for ≥2 doses and/or

ii) ≥1 regimen containing ≥1 cytotoxic agent (e.g., bendamustine, chlorambucil, cyclophosphamide, cytarabine, doxorubicin) administered for ≥2 cycles, and/or

iii) ≥1 regimen containing yttrium^{90}-ibritumomab tiuxetan (Zevalin®) or iodine^{131}-tositumomab (Bexxar®).

3. Presence of radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (defined as the presence of a ≥2.0 cm lesion as measured in the longest dimension by computed tomography [CT] scan). Note: Not applicable to subjects with WM and MM.

4. Absolute neutrophil count (ANC) ≥1.5 x 10^9/L or platelet count ≥100 x 10^9/L unless due to disease involvement in the bone marrow.

All Parts:

5. Men and women ≥18 years of age.

6. Documented active disease.

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

8. Females must agree to use highly effective forms of contraception during the study and for 2 days after the last dose of acalabrutinib and 90 days after the last dose of APC-319, whichever is longer, if sexually active and able to bear children. Highly effective forms of contraception are defined in Section 3.11.4.
9. Males must agree to use highly effective forms of contraception while taking ACP-319 and for 90 days after their last dose of ACP-319, if sexually active and able to beget children. Males must also refrain from sperm donation during the study and for 90 days after the last dose of ACP-319.
10. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty.
11. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local patient privacy regulations).

Part 2 Additional disease entry criteria:

12. DLBCL (GCB): Confirmed diagnosis of DLBCL with disease characterized as GCB subtype by immunohistochemistry (Hans et al. 2004 or Choi et al. 2009) and meeting the rest of the criteria as defined above, including characterization as de novo DLBCL.
13. Richter's syndrome: Confirmed diagnosis of previously treated CLL/SLL with previously untreated and biopsy-proven DLBCL due to Richter transformation and meeting the rest of the criteria as defined above.
14. MM: Confirmed diagnosis of MM, which has relapsed after, or been refractory to ≥1 prior therapy for MM and is progressing at the time of study entry and meeting the rest of the criteria as defined above.
15. B-ALL: Confirmed diagnosis of previously treated B-ALL and meeting the rest of the criteria as defined above.

3.3.2 Exclusion Criteria

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

All Parts:

1. Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject has been

disease free for ≥2 years or which will not limit survival to <2 years. Note: These cases must be discussed with 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 and/or ACP-319, or put the study outcomes at undue risk.
3. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification.
4. Malabsorption syndrome, disease significantly affecting gastrointestinal (GI) function, resection of the stomach, extensive small bowel resection that is likely to affect absorption, symptomatic inflammatory bowel disease, partial or complete bowel obstruction, or gastric restrictions and bariatric surgery such as gastric bypass.
5. CNS involvement by lymphoma/leukemia.
6. Any therapeutic antibody within 4 weeks of first dose of study drug.
7. The time from the last dose of the most recent chemotherapy or experimental therapy to the first dose of study drug is <5 times the half-life of the previously administered agent(s).
8. Any prior therapy with BTK, PI3Kδ, or SYK inhibitors or BCL-2 inhibitors (e.g., venetoclax/ABT-199). Note: Prior treatment with reversible, noncovalent BTK inhibitors is not excluded on this protocol.
9. Ongoing immunosuppressive therapy, including systemic or enteric corticosteroids for treatment of lymphoid cancer or other conditions. Note: Subjects may use topical or inhaled corticosteroids or low-dose steroids (≤10 mg of prednisone or equivalent per day) as therapy for comorbid conditions. During study participation, subjects may also receive systemic or enteric corticosteroids as needed for treatment-emergent comorbid conditions.
10. Use of a strong inhibitor or inducer of cytochrome P450 (CYP)3A (see Appendix 3) within 7 days before dose of study drug or expected requirement for use of a CYP3A inhibitor or inducer during the first 28 days of administration of study drugs.
11. Remains not applicable for this amendment.
12. Known history of HIV, serologic status reflecting active hepatitis B or C infection, or any uncontrolled active systemic infection.

a) Subjects who are hepatitis B core antibody (anti-HBc) positive and who are surface antigen negative will need to have a negative polymerase chain reaction (PCR) result before enrollment. Those who are hepatitis B surface antigen (HbsAg) positive or hepatitis B PCR positive will be excluded.
b) Subjects who are hepatitis C antibody positive will need to have a negative PCR result before enrollment. Those who are hepatitis C PCR positive will be excluded.

13. Major surgery within 4 weeks before first dose of study drugs. Note: If a subject had major surgery, they must have recovered adequately from any toxicity and/or complications from the intervention before the first dose of study drug.
14. History of stroke or intracranial hemorrhage within 6 months before the first dose of study drugs.
15. Ongoing, drug-induced liver injury, alcoholic liver disease, nonalcoholic steatohepatitis, primary biliary cirrhosis, ongoing extrahepatic obstruction caused by cholelithiasis, cirrhosis of the liver, or portal hypertension.
16. History of or ongoing drug-induced pneumonitis.
17. Part 2 only: ANC $<0.5 \times 10^9$/L or platelet count $<50 \times 10^9$/L unless due to disease involvement in the bone marrow.
18. 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].
19. Significant screening ECG abnormalities including left bundle-branch block, second-degree AV block type II, third-degree AV block, Grade ≥2 bradycardia, and QTc >480 msec.
20. Breastfeeding or pregnant.
21. Concurrent participation in another therapeutic clinical trial.
22. History of bleeding diathesis (e.g., hemophilia or von Willebrand disease).
23. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon) within 7 days of first dose of study drug.
24. Requires treatment with proton-pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). Subjects receiving proton-pump inhibitors who switch to H2-receptor antagonists or antacids are eligible for enrollment to this study.
25. Total bilirubin >1.5 x upper limit of normal (ULN), or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3.0 x ULN.
26. Serum amylase >1.5 x ULN or serum lipase >1.5 x ULN.

27. Presence of a GI ulcer diagnosed by endoscopy within 3 months before screening.
28. Concomitant use of medicines known to cause QT prolongation or Torsades de pointes within 7 days of starting study drug (see Appendix 2).
29. Active cytomegalovirus (CMV) infection (positive CMV immunoglobulin [Ig] M and/or positive PCR result).

3.3.3 Replacement of Subjects

Any subject who does not complete study therapy through Cycle 2 for reasons other than the occurrence of a Cycle 1 DLT in Part 1 may be replaced at the discretion of the study investigators and sponsor. Should the decision be made to replace a subject, the replacement subject will be assigned to the same treatment cohort as the original subject.

3.3.4 Enrollment Procedures

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

- The study center will notify the sponsor when a clinically eligible subject is identified and is ready to screen, to ensure enrollment availability on the study.
- After the subject has signed and dated the ICF and all screening procedures have been completed, the site must submit the completed Enrollment Confirmation Form and supporting documents as required in the Enrollment Confirmation Form to the sponsor for review and approval before enrollment.
- After subject eligibility has been reviewed and confirmed by the medical monitor, the subject can be officially enrolled into the study. The sponsor will aim to fax/email a completed Enrollment Confirmation Form with the cohort allocation information to the study center within 24 hours after receiving all required documentation. The enrollment date will be the date that the sponsor confirms enrollment.

Treatment must begin within 21 days of the start of the screening visit after the site has received the cohort allocation from the sponsor.

3.4 STUDY DRUGS

3.4.1 Premedications

No specific premedications or supporting medications are required in conjunction with acalabrutinib or ACP-319 administration.

Tumor lysis syndrome has not been observed, to date, with either acalabrutinib or ACP-319. Whether there could be an increased likelihood of tumor lysis syndrome when coadministering acalabrutinib and ACP-319 is unknown. Investigators are at liberty to

consider additional monitoring and prophylaxis for tumor lysis syndrome according to local practices (see Section 3.10).

As general precautions considering the subject population, institution of antibiotic prophylaxis for *Pneumocystis (carinii) jiroveci* and use of intravenous immunoglobulin (IVIG) may be considered in selected study subjects (see Section 3.10).

3.4.2 Formulation, Packaging, and Storage

Acalabrutinib and ACP-319 are manufactured according to current Good Manufacturing Practice regulations and will be provided to the investigational site by Acerta Pharma or designee. They should be stored according to the instructions on the label that is affixed to the package containing each respective drug product. Both drug products are provided as capsules intended for oral administration.

Acalabrutinib will be provided in white, high-density polyethylene bottles.

ACP-319 will be provided in high-density polyethylene bottles.

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

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3.4.3 Administration of Study Drug

Investigators are prohibited from supplying acalabrutinib or ACP-319 to any subjects not properly enrolled in this study. The investigator must ensure that subjects receive acalabrutinib or ACP-319 only from personnel who fully understand the procedures for administering the drug.

Both drugs are intended to be administered orally BID with 8 ounces (approximately 240 mL) of water. Subjects receiving acalabrutinib (and previously ACP-319) combination therapy should be instructed to take each dose of both study drugs at the same time on an empty stomach, defined as no food 2 hours before and 1 hour after dosing. Subjects receiving acalabrutinib monotherapy are not required to fast before and after acalabrutinib administration. The capsules should be swallowed intact. Subjects should not attempt to open the capsules or dissolve them in water. Doses should be taken 12 hours (± 60 minutes) apart.

If a dose is not taken within the allowed window, it can be taken up to 3 hours after the scheduled time with a return to the normal schedule the same or the following day. If the delay is >3 hours, the dose should not be taken, and the subject should take the next dose at the next scheduled time.

Guidance on coadministration of acalabrutinib with agents that affect gastric pH is provided in Section 3.11.3.

3.4.4 Assuring Subject Compliance

Subjects will receive their morning dose in the clinic on Cycle 1 Days 1, 8, 15, 22, and 28, Cycle 2 Days 15 and 28, and Cycles 3 and 4 Day 28. 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 drug diary to record the specific time each dose was taken and to record reasons for any missed doses.

Subject compliance will be assessed at every visit. The subject will be instructed to bring the diary and any remaining capsules to the clinic at their next visit. The study staff will review the diary and ask the subject if all of the capsules were administered. Any remaining or returned capsules will be counted and recorded as described in Section 7.7. Returned capsules must not be re-dispensed to another subject.

3.5 STUDY DRUG DOSING

Regimens:

Part 1:

The acalabrutinib dose will be fixed at 100 mg BID. The ACP-319 dose will be escalated as follows:

Cohort 1: Acalabrutinib 100 mg BID + ACP-319 25 mg BID continuously
Cohort 2: Acalabrutinib 100 mg BID + ACP-319 50 mg BID continuously
Cohort 3: Acalabrutinib 100 mg BID + ACP-319 100 mg BID continuously

Twenty-eight days of study drug administration is defined as 1 cycle. Each dosing cohort will be enrolled sequentially with 6 subjects per cohort. If ≤1 DLT (see Section 3.7 for definition) is observed in the cohort during Cycle 1, escalation to the next cohort will proceed. If ≥2 DLTs are observed during Cycle 1, dosing at that dose and higher will be suspended and the MTD will be established as the previous cohort. The MTD is defined as the largest daily dose for which fewer than 33% of the subjects

experience a DLT during Cycle 1. Escalation will end with Cohort 3 or sooner if the MTD is reached in an earlier cohort.

Note: Under Amendment 3 of this protocol, subjects with CLL/SLL will receive acalabrutinib monotherapy (100 mg BID).

Part 2:

Acalabrutinib 100 mg BID and ACP-319 50 mg BID continuously.

Note: Under Amendment 3 of this protocol, subjects with CLL/SLL will receive acalabrutinib monotherapy (100 mg BID).

3.6 DURATION OF THERAPY

Subjects will continue to receive study treatment until the occurrence of any of the events described in Section 3.12.

Subjects showing clinical benefit and who are tolerating study treatment may remain on study until the end of study, defined as 36 months after the last subject is enrolled. Subjects who are still on treatment at the end of the study and deriving clinical benefit from acalabrutinib monotherapy may be eligible to enroll in a rollover or safety extension study of acalabrutinib monotherapy (see Section 3.0).

3.7 ASSESSMENT OF DOSE-LIMITING TOXICITY

In Part 1, a DLT will be defined as the occurrence of any of the following ACP-319-related AEs:

1. Any Grade ≥3 nonhematologic toxicity (except Grade 3 nausea, vomiting, or diarrhea that respond to supportive therapy)
2. Any of the following hematologic toxicities (for CLL):
   a. Grade 4 neutropenia lasting >7 days
   b. Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia with bleeding, or any requirement for platelets transfusion
   c. Grade 3 febrile neutropenia (temperature ≥38.5°C)
   d. Grade 4 anemia, unexplained by underlying disease
3. Dosing delay due to toxicity for >28 consecutive days

3.8 DOSING DELAYS AND MODIFICATIONS

Subjects should be followed closely for AEs or laboratory abnormalities that might indicate acalabrutinib- or ACP-319-related toxicity. If a subject experiences a treatment-related DLT or other AE requiring dose modification during the course of

therapy, then acalabrutinib, ACP-319, or both drugs should be held, as necessary, until the AE resolves or stabilizes to an acceptable degree.

When restarting treatment, study drugs should be re-introduced in a staggered fashion, after discussion with the medical monitor. If both drugs were withheld, acalabrutinib (at the original or modified dose) should be given alone for at least 7 days, and the subject monitored closely for recurrence of AEs, before adding ACP-319.

3.8.1 Dose Delays

Treatment with acalabrutinib, ACP-319, or both, should be held for any unmanageable, potentially study drug-related toxicity that is Grade ≥3 in severity. Any other clinically important events where dose delays may be considered appropriate by the investigator must be discussed with the medical monitor.

Study drug may be held for a maximum of 28 consecutive days from expected dose due to toxicity. Study treatment should be discontinued in the event of a toxicity lasting >28 days, unless reviewed and approved by the medical monitor.

Note: Temporary withholding of study drug for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms, which may not indicate definitive disease progression. Refer to Section 3.12 for more information on assessing disease progression under these circumstances.

3.8.2 Dose Modification and Discontinuation

The actions in Table 3-1 should be taken for any Grade 4 toxicity or unmanageable Grade 3 toxicity. In addition, the actions in Table 3-1 should be taken when modification of the acalabrutinib dose is recommended for specific treatment-related AEs as listed in Table 3-2.

Table 3-1. Dose Modification Actions for Acalabrutinib

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

Abbreviations: BID = twice daily; QD = once daily.

Dependent on the subject's initial dose level, subjects who cannot tolerate a rechallenge at the lowest recommended dosages of acalabrutinib and/or ACP-319 should be removed from study treatment.

If acalabrutinib and/or ACP-319 are reduced for apparent treatment-related toxicity, the doses need not be re-escalated, even if there is minimal or no toxicity with the reduced doses. However, if the subject tolerates a reduced dose of acalabrutinib and/or ACP-319 for ≥4 weeks then the dose may be increased to the next higher dose level at the discretion of the investigator and after discussion with the medical monitor. Such reescalation may be particularly warranted if further evaluation reveals that the AE that led to the dose reduction was not treatment related.

ACP-319 should be held in subjects with evidence of CMV infection of any grade or viremia (positive PCR or antigen test). ACP-319 may be restarted once the subject is PCR negative, as per investigator discretion. If ACP-319 is resumed, monitor (by PCR or antigen test) for CMV reactivation at least monthly and consider administering pre-emptive CMV therapy. Refer to Section 4.1.24 for monthly CMV testing.

ACP-319 should be held in subjects with suspected *Pneumocystis jirovecii* pneumonia (PJP) infection of any grade. ACP-319 should be discontinued permanently in subjects with active or confirmed PJP infection. Refer to Section 3.10.4 for PJP infection prophylaxis. Whenever possible, any dose adjustment of study drugs should be discussed between the investigator and the medical monitor before implementation. The appropriate clinic staff should dispense the study drug for the new dose level and instruct the subject/caregiver about the change in dose level. Any changes to the dosing regimen must be recorded on the appropriate electronic case report form (eCRF).

3.9 MANAGEMENT OF SPECIFIC AEs

Recommendations for modifications of the dosing regimens based on the drug and the type and severity of AEs or laboratory abnormalities are provided in Table 3-2. The recommendations provided in Table 3-2 comprise only guidelines; variations from these recommendations may be warranted based on an investigator's individual judgment in considering potential risks, benefits, and therapeutic alternatives available to each subject. Whenever possible, any interventions for potential treatment-related AEs should be discussed between the investigator and the medical monitor before implementation.

Please refer to Section 4.1.9 for dose modifications based on QTc AEs.

Table 3-2. Recommendations for Acalabrutinib and ACP-319 Dose Modifications Based on Type and Severity of Treatment-Related Adverse Events or Laboratory Abnormalities

NCI CTCAE Grade	Recommendation	
	Acalabrutinib	**ACP-319**
Gastrointestinal Inflammation/Diarrhea		
Grade 1 Mild diarrhea: Increase of < 4 stools per day over baseline	Provide antidiarrheal (e.g., loperamide) and maintain current acalabrutinib dose level and schedule.	Provide antidiarrheal (e.g., loperamide) and maintain current ACP-319 dose level and schedule.
Grade 2 Moderate diarrhea: Increase of 4–6 stools per day over baseline	Provide antidiarrheal (e.g., loperamide). Withhold acalabrutinib until Grade ≤1. Resume acalabrutinib at current dose level. If rechallenge results in recurrence, may resume at initial or lower dose level at investigator discretion (if applicable). Consider addition of anti-inflammatory (e.g., sulfasalazine, budesonide).	Provide antidiarrheal (e.g., loperamide) and maintain current ACP-319 dose level and schedule. Monitor at least weekly until resolved. Consider addition of anti-inflammatory (e.g., sulfasalazine, budesonide).
Grade 3 Severe diarrhea: Increase of ≥7 stools per day over baseline	Provide antidiarrheal (e.g., loperamide). Withhold acalabrutinib until Grade ≤1. Resume at lower dose level (if applicable). Consider addition of anti-inflammatory (e.g., sulfasalazine, budesonide).	Provide antidiarrheal (e.g., loperamide). Withhold ACP-319 until Grade ≤1. Resume at lower dose level (if applicable). Consider addition of anti-inflammatory (e.g., sulfasalazine, budesonide).
Grade 4 Life-threatening diarrhea	Provide antidiarrheal (e.g., loperamide). Withhold acalabrutinib until Grade ≤1. May resume at lower dose level (if applicable) or discontinue acalabrutinib at investigator discretion. Consider addition of anti-inflammatory (e.g., sulfasalazine, budesonide).	Discontinue ACP-319 permanently.
Hepatic Adverse Events (elevations in ALT, AST, or bilirubin)		
Grade 1 (ALT/AST ≤3 x ULN) (Bilirubin ≤1.5 x ULN)	Maintain current dose level and schedule. Monitor ALT, AST, ALP, and bilirubin at least 1x per week.	Maintain current dose level and schedule. Monitor ALT, AST, ALP, and bilirubin at least 1x per week.
Grade 2 (ALT/AST >3-5 x ULN) (Bilirubin >1.5- ≤ 3 x ULN)		

Table 3-2. Recommendations for Acalabrutinib and ACP-319 Dose Modifications Based on Type and Severity of Treatment-Related Adverse Events or Laboratory Abnormalities

	Recommendation	
NCI CTCAE Grade	**Acalabrutinib**	**ACP-319**
Grade 3 (ALT/AST >5-20 x ULN) (Bilirubin >3-10 x ULN)	Withhold or continue acalabrutinib (at investigator discretion, after discussion with the medical monitor). Monitor ALT, AST, ALP, and bilirubin at least 1x per week. After 7 days if hepatic enzymes appear to be improving and acalabrutinib was withheld, restart acalabrutinib at current dose level.	Withhold ACP-319. Monitor ALT, AST, ALP, and bilirubin at least 1x per week until all abnormalities have returned to Grade ≤1. Recommend treating with high dose oral or IV corticosteroids (at a dosage of 40 mg prednisone or equivalent QD) for at least 48 hours; when all abnormalities have returned to Grade ≤1, recommend tapering steroids over no <4 weeks. Once abnormalities have returned to Grade ≤1, ACP-319 may resume at initial or lower dose level (if applicable).
Grade 4 (ALT/AST >20 x ULN) (Bilirubin >10 x ULN)	See recommendations for Grades 2 or 3	Discontinue ACP-319 permanently.
Pneumonitis (dyspnea, cough, hypoxia and/or diffuse interstitial pattern or ground-glass opacities on chest CT and no obvious infectious cause)		
Grade 1	Maintain current dose level and schedule. Consider pneumocystis prophylaxis.	Discontinue ACP-319 permanently.
Grade 2	Withhold acalabrutinib until Grade ≤1, consider systemic corticosteroids and pneumocystis treatment. May resume at initial or lower dose level (if applicable) at investigator discretion.	Discontinue ACP-319 permanently.
Grade ≥≥3	Withhold acalabrutinib until Grade ≤1, consider systemic corticosteroids and consider pneumocystis treatment. May resume at lower dose level (if applicable) or discontinue acalabrutinib at investigator discretion.	Discontinue ACP-319 permanently.

Table 3-2. Recommendations for Acalabrutinib and ACP-319 Dose Modifications Based on Type and Severity of Treatment-Related Adverse Events or Laboratory Abnormalities

NCI CTCAE Grade	Recommendation	
	Acalabrutinib	**ACP-319**
Neutropenia		
Grade ≤2	Maintain current dose level and schedule.	Maintain current dose level and schedule.
Grade 3	Maintain current dose level and schedule.	Maintain current dose level and schedule. Monitor ANC at least 1x per week.
Grade 4	Maintain current dose level and schedule and monitor ANC at least 1x per week. If Grade 4 neutropenia lasts for >7 days (neutrophil growth factors are permitted per ASCO guidelines [Smith et al. 2015b] and use must be recorded on the CRF), modify dose as instructed in Table 3-1.	Withhold ACP-319. Monitor ANC at least 1x per week until ANC ≥0.5 x 10^9/L, then resume ACP-319 at lower dose level (if applicable).
Thrombocytopenia		
Grade ≤2	Maintain current dose level and schedule.	Maintain current dose level and schedule.
Grade 3	If no significant bleeding, maintain current dose level and schedule. In the presence of significant bleeding, modify dose as instructed in Table 3-1.	Maintain current dose level and schedule. Monitor PLT at least 1x per week.
Grade 4	Modify dose as instructed in Table 3-1.	Withhold ACP-319. Monitor PLT at least 1x per week until PLT ≥25 x 10^9/L, then resume ACP-319 at lower dose level (if applicable).
Rash		
Grade 1	Maintain current dose level and schedule.	Maintain current dose level and schedule.
Grade 2	Maintain current dose level and schedule.	Withhold ACP-319 until Grade ≤1, consider systemic corticosteroids. May resume ACP-319 at initial or lower dose (if applicable) at investigator discretion.

Table 3-2. Recommendations for Acalabrutinib and ACP-319 Dose Modifications Based on Type and Severity of Treatment-Related Adverse Events or Laboratory Abnormalities

NCI CTCAE Grade	Recommendation	
	Acalabrutinib	**ACP-319**
Grade = 3 or 4	Withhold acalabrutinib until Grade ≤1, consider systemic corticosteroids. May resume acalabrutinib at initial or lower dose level (if applicable) at investigator discretion.	Discontinue ACP-319 permanently.
QTC Interval Prolongation		
		Refer to Section 4.1.9.
Other Nonhematologic Adverse Events		
Grade ≤2	Maintain current dose level and schedule.	Maintain current dose level and schedule.
Grade = 3 or 4	Withhold acalabrutinib until Grade ≤1. May resume acalabrutinib at initial or lower dose level (if applicable) or discontinue acalabrutinib at investigator discretion.	Withhold ACP-319 until Grade ≤1. May resume ACP-319 at lower dose level (if applicable) or discontinue ACP-319 at investigator discretion. If toxicity recurs upon rechallenge, discontinue ACP-319 permanently.

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; ASCO = American Cancer Society; AST = aspartate aminotransferase; CRF = case report form; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NCI = National Cancer Institute; PLT = platelet count; QD = once daily; ULN = upper limit of normal.

3.9.1 Gastrointestinal Inflammation/Diarrhea

In Amgen Study #20101262, 6 subjects treated with ACP-319 developed colitis, including 2 serious cases determined to be of infectious origin (enterocolitis and *Clostridium difficile*). Four cases of Grade 2 or Grade 3 colitis without infectious etiology occurred in subjects treated with 400 mg QD. AEs of colitis resolved with dose reductions of ACP-319 to lower dose levels (200 to 300 mg) in subjects in the 400-mg dose group.

Other studies of PI3Kδ inhibitors have recommended that for subjects who develop persistent diarrhea, causes related to concomitant medications or GI infection should be considered and eliminated. Depending upon the clinical circumstances, endoscopy and biopsy may be warranted. In such subjects, after drug discontinuation and resolution of symptoms, rechallenge with PI3Kδ inhibitors has resulted in recurrence of symptoms in some but not all subjects and has not been associated with other severe AEs. Subjects

have responded well to administration of enteric corticosteroids (e.g., budesonide) or sulfasalazine (AZULFIDINE®) while continuing on PI3Kδ inhibitors.

Thus, depending upon the type and severity of the initial GI event, rechallenge with study drug and appropriate support care may be warranted if continued drug administration offers the potential for clinical benefit (Table 3-2). Administer appropriate antibiotics, including vancomycin and/or metronidazole if required for *C difficile* infections. Subjects should be advised to report any new or worsening abdominal pain, onset of fever, chills, nausea, or vomiting.

3.9.2 Elevated Liver Function Tests and Immune-Mediated Hepatitis

In subjects with lymphoid malignancies, reversible serum ALT/AST elevations have been observed (Furman et al. 2010, Kahl et al. 2010) with idelalisib. In these subjects, onset has typically occurred within 2 to 16 weeks of starting the PI3Kδ inhibitor therapy.

Among subjects receiving ACP-319 with Grade 1 to 2 ALT/AST abnormalities, continued dosing has been possible; transaminase values commonly resolve despite continued PI3Kδ inhibitor treatment. For those with Grade 3 to 4 ALT/AST elevations, drug interruption has resulted in resolution over 2 to 6 weeks. Successful rechallenge at lower dose levels of PI3Kδ inhibitor has been achieved in most subjects. Thus, in subjects with uncomplicated hepatic laboratory abnormalities, the instructions in Table 3-2 should be followed in an attempt to maximize the potential that subjects who appear to be benefiting can continue with study drug treatment.

In selected subjects who experience more complicated hepatic AEs, further workup may be warranted, particularly in subjects who first experience a serum ALT/AST elevation ≥12 weeks from the start of study drug therapy, who have an elevation in serum bilirubin concentration or change in coagulation parameters, or who have other characteristics that suggest a change in liver function. Further workup may include the following: obtaining a history of recent symptoms/illnesses and of relevant past history (e.g., history of hepatitis or of hepatitis A or hepatitis B vaccination); obtaining information regarding concomitant drug use (prescription and nonprescription medications, dietary supplements, alcohol, illicit drugs, special diets); questioning the subject regarding potential exposure to environmental toxins; ruling out viral hepatitis A, B, C, D (if hepatitis B is positive), and E, Epstein-Barr virus, CMV, autoimmune hepatitis, alcoholic hepatitis, nonalcoholic steatohepatitis, hypoxic/ischemic hepatopathy, and biliary tract disease; obtaining additional tests to evaluate liver function (e.g., prothrombin time [PT], activated partial thromboplastin time, international normalized ratio [INR], albumin); and

considering gastroenterology or hepatology consultation (Food and Drug Administration. Guidance for industry. Drug-induced liver injury: premarketing clinical evaluation. 2009 Jul). Hepatic AEs that require additional workup should be discussed with the medical monitor.

Hepatitis has been reported in subjects treated with the combination of acalabrutinib and ACP-319. Subjects with hepatitis should be carefully monitored, and dose modification or interruption of either acalabrutinib or ACP-319 or both may be indicated. Refer to Table 3-2 for additional information on management of hepatic AEs.

Subjects should be monitored for increases in liver biochemistry indicating potential Hy's law (PHL) or Hy's law (HL). The investigator is responsible for determining whether a subject meets PHL criteria at any point during the study. The process to be followed in identifying and reporting cases of PHL and HL is summarized in Appendix 6.

3.10 CONCOMITANT THERAPY

3.10.1 Permitted Concomitant Therapy

Anti-emetics are permitted if clinically indicated. Standard supportive care medications are permitted as per institutional standards.

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

For subjects at risk for pneumonitis: In selected subjects (e.g., those with a history of recurrent pneumonias), anti-infectious prevention should be considered. Initiation of antibiotic prophylaxis against pneumocystis infection (e.g., with trimethoprim-sulfamethoxazole, dapsone, aerosolized pentamidine, or atovaquone) beginning before study drug administration may be warranted. Such supportive care may also offer the benefit of reducing the risk for other bacterial infections (Stern et al. 2014). Prophylaxis with intravenous Ig may be appropriate in subjects with low Ig levels (Raanani et al. 2009). Local practices or guidelines regarding infection prophylaxis may be followed.

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

3.10.2 Prohibited or Restricted Concomitant Therapy

Any chemotherapy, immunotherapy, kinase inhibitors, bone marrow transplant, experimental therapy, or radiotherapy for treating lymphoid cancer are prohibited.

Localized, short courses of radiotherapy are allowed for the treatment of lesions unrelated to the disease under study, if approved by the medical monitor.

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

At study entry, subjects may be using topical or inhaled corticosteroids or low-dose steroids (≤10 mg of prednisone or equivalent per day) as therapy for comorbid conditions but use of corticosteroids as therapy of the lymphoid cancer is not permitted. During study participation, subjects may also receive systemic or enteric corticosteroids at any required dosage as needed for treatment-emergent comorbid conditions such as treatment-emergent colitis or pneumonitis.

Use of omeprazole, esomeprazole, lansoprazole, or any other proton-pump inhibitors is prohibited at study entry. 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 GI condition and a potential risk of decreased exposure to acalabrutinib.

Subjects should avoid the use of calcium carbonate-containing drugs or supplements for a period of at least 2 hours before and at least 2 hours after taking acalabrutinib. 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.

The concomitant use of strong inhibitors/inducers of CYP3A (see Appendix 3) 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. Conversely concomitant administration of a strong inducer of CYP3A has the potential to decrease exposure of ACP-319 or acalabrutinib and could reduce the efficacy of the study drugs. For additional information on drugs with potential drug-drug interactions, refer to Section 3.11.3.

Use of medications known to prolong QTc interval or that may be associated with Torsades de pointes (see Appendix 2) are prohibited within 7 days of starting study drug and during Day 1 to 28 inclusive of Cycle 1.

3.10.3 Concomitant Medication for Subjects with MM

For subjects with MM, the first 6 subjects enrolled will receive acalabrutinib 100 mg BID and ACP-319 at the dose level determined from the escalation portion of the study. The last 6 subjects enrolled will receive acalabrutinib 100 mg and ACP-319 at the same level as the first 6 subjects and will concomitantly receive 40 mg dexamethasone once weekly. This study will use commercially available dexamethasone. Refer to the appropriate dexamethasone package insert for storage and handling instructions and warnings and precautions.

3.10.4 Required Concomitant Medications

Serious and fatal infections have occurred with idelalisib (a drug similar to ACP-319) including opportunistic infections such as *Pneumocystis jirovecii* pneumonia (PJP) and CMV (ZYDELIG [Summary of Product Characteristics]). Therefore, due to possible risk of class effects, prophylaxis for PJP in accordance with local guidelines and institutional standards should be administered to all subjects throughout ACP-319 treatment, and for a period of 2 to 6 months after the last dose of ACP-319. The duration of post-treatment prophylaxis should be based on clinical judgment and may take into account a subject's risk factors such as concomitant corticosteroid treatment and prolonged neutropenia. CMV testing will be required for subjects receiving ACP-319 treatment (see Section 4.1.24).

3.11 RISKS ASSOCIATED WITH STUDY DRUGS

3.11.1 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.

Hemorrhage

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

The mechanism for hemorrhage is not well understood. Patients receiving antithrombotic agents may be at increased risk of hemorrhage. Use caution with antithrombotic agents and consider additional monitoring for signs of bleeding when concomitant use is medically necessary. Consider the benefit-risk of withholding acalabrutinib for at least 3 days pre- and post-surgery. Subjects with hemorrhage

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

Infections

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

Consider prophylaxis in subjects who are at increased risk for opportunistic infections. Subjects should be monitored for signs and symptoms of infection and treated as medically appropriate. Refer to Section 3.11.6, Section 4.1.13, and Appendix 6 for additional information and monitoring guidance for viral hepatitis and Section 3.11.7 for additional information and management guidance for signs and symptoms of PML.

Cytopenias

Treatment-emergent 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 (Appendix 5) and as medically appropriate. Please refer to Section 3.8 for study drug modification guidance. Subjects with cytopenias should be managed according to institutional guidelines with maximal supportive care and diagnostic evaluations as clinically indicated. Subjects should be closely monitored as appropriate.

Second Primary Malignancies

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. Please refer to Section 6.3.3 for reporting guidance.

Atrial Fibrillation

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

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

3.11.2 Dietary Restrictions

Because acalabrutinib is metabolized by CYP3A (refer to the acalabrutinib Investigator Brochure for details), subjects should be strongly cautioned against the use of herbal remedies or dietary supplements (in particular, St John's wort, which is a potent CYP3A inducer).

Subjects should be encouraged to follow instructions related to eating relative to study drug administration (Section 3.4.3).

3.11.3 Drug-Drug Interactions

The concomitant use of strong inhibitors/inducers of CYP3A with acalabrutinib should be avoided when possible (see Appendix 3). If a subject requires short-term treatment with a strong CYP3A inhibitor (such as anti-infectives for up to 7 days), interrupt acalabrutinib treatment. Refer to Table 3-3 for dose modifications due to required short-term use of moderate or strong CYP3A inhibitors.

Avoid coadministration of strong CYP3A inducers. If a subject requires treatment with a strong CYP3A inducer, increase the acalabrutinib dose to 200 mg BID during concomitant administration with the strong inducer and return to recommended dose of 100 mg BID after stopping the strong CYP3A inducer.

Use of proton-pump inhibitors, H2 receptor antagonists, or antacids while taking acalabrutinib has the potential to decrease acalabrutinib exposure. If treatment with a gastric acid reducing agent is required, consider using an H2-receptor antagonist (2 hours after acalabrutinib) or antacid (2 hours before or 2 hours after acalabrutinib). Avoid coadministration with proton-pump inhibitors.

Table 3-3. Instructions for Coadministration of Drugs with Acalabrutinib

Coadministered Drug	Acalabrutinib
Strong CYP3A inhibitor	Avoid concomitant use with acalabrutinib. If the inhibitor will be used short-term (such as anti-infectives for up to 7 days), interrupt acalabrutinib.
Moderate CYP3A inhibitor	Decrease acalabrutinib dose to 100 mg QD
Strong CYP3A inducer	Avoid concomitant use. If concomitant use cannot be avoided, increase acalabrutinib dose to 200 mg BID.
Moderate CYP3A inducer	No change
P-gp inhibitor	No change
BCRP inhibitor	No change
Narrow therapeutic index P-gp substrate	No change
Bile acid sequestrants	No change
Statin (OATP substrate)	No change
Proton pump inhibitors	Avoid concomitant use.
H2-receptor antagonists	Take acalabrutinib 2 hours before taking a H2-receptor antagonist.
Antacids	Separate dosing by at least 2 hours.

BCRP = breast cancer resistance protein; BID = twice daily; CYP = cytochrome P450; H = histamine; OATP = organic-anion-transporting polypeptide; P-gp = P-glycoprotein; QD = once daily.

3.11.4 Reproductive Toxicity

Women of Childbearing Potential

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

Subjects of Non-Reproductive Potential

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

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

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

Highly Effective Methods of Contraception

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

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

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

Abstinence (relative to heterosexual activity) can only be used as the sole method of contraception if it is consistently employed during the entire period of risk associated with the study treatments as the subject's preferred and usual lifestyle.

Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, and post-ovulation methods) and withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. Female condom and male condom should not be used together as an effective method of contraception.

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

3.11.5 Overdose Instructions

For any subject experiencing an acalabrutinib overdose (ingestion of more than the recommended dosage), 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.

The medical monitor must be contacted if a study drug overdose occurs.

3.11.6 Hepatitis B Virus Reactivation

Serious or life-threatening reactivation of viral hepatitis may occur in subjects treated with acalabrutinib, obinutuzumab, or rituximab. Increased risk of infections including viral hepatitis may also occur in subjects treated with standard chemotherapy including cyclophosphamide and bendamustine. Refer to Section 4.1.13 for details on viral hepatitis screening and monitoring for this study.

3.11.7 Progressive Multifocal Leukoencephalopathy

Serious or life-threatening occurrence of PML may occur in subjects treated with acalabrutinib, obinutuzumab, or rituximab. Increased risk of infections including PML may also occur in subjects treated with standard chemotherapy including fludarabine and cyclophosphamide.

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

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

- Neurologic consultation
- Brain magnetic resonance imaging
- PCR analysis for John Cunningham or JC virus DNA in cerebrospinal fluid

If PML is confirmed, permanently discontinue study treatment (as applicable, based on risks in the acalabrutinib Investigator Brochure or local prescribing information).

3.12 WITHDRAWAL OF SUBJECTS FROM STUDY TREATMENT

All study participants may receive acalabrutinib as long as they are safely benefitting; however:

- The investigator, in consultation with the medical monitor, may withdraw any subject from study treatment, if, in the investigator's opinion, it is not in the subject's best interest to continue.
- Any subject has the right to withdraw from the study at any time.

- Any subject whose study treatment is delayed (i.e., has not received acalabrutinib) for >28 consecutive days due to study drug-related toxicity should be withdrawn from study treatment, unless reviewed and approved by the medical monitor.
- Any subject who has confirmed objective evidence of cancer progression while receiving study treatment at the highest individual tolerable dose level allowed in the protocol (see Section 3.5 and Section 3.8) should be withdrawn from the study treatment. Note: If there is uncertainty regarding whether there is cancer progression, the subject may continue study treatment and remain under close observation (e.g., evaluated at 4- to 8-week intervals) pending confirmation of progression. **Transient worsening of disease during temporary interruption of study therapy (e.g., for drug-related toxicity, surgery, or intercurrent illness) may not indicate disease progression**. In such circumstances, and if medically appropriate, subjects may resume therapy and relevant clinical, laboratory, and/or radiographic assessments should be done to document whether tumor control can be maintained or whether actual disease progression has occurred.
- Any subject who is unable to tolerate a rechallenge at the lowest recommended dose of acalabrutinib (see Section 3.8) should be discontinued from the study treatment unless continued therapy is permitted by the medical monitor. Note: If medically appropriate, subjects may continue with protocol-specified therapy for acalabrutinib if the therapeutic agent continues to be tolerated.
- 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.
- Any subject who becomes pregnant should be removed from study treatment.
- Any subject who becomes significantly noncompliant with study drug administration, study procedures, or study requirements should be withdrawn from study treatment in circumstances that increase risk or substantially compromise the interpretation of study results.

Subjects who discontinue study therapy will continue on study for safety (Section 4.3), disease progression, and time-to-next therapy (Section 4.4) for their lymphoid cancer unless they withdraw consent for further follow-up. Thus, all subjects receiving ≥1 dose of study drug will be followed during the immediate post-therapy period unless the subject withdraws consent for such follow-up to be conducted. The date the subject is

withdrawn from study treatment or from the study (including post-therapy follow-up) and the reason for discontinuation will be recorded and also should be described on the appropriate CRF.

3.13 REASONS FOR STUDY EXIT

Reasons for study exit include:

- Subject's withdrawal of consent from study
- Decision by sponsor to terminate the study
- Disease progression
- Start of alternative anticancer therapy
- Subject lost to follow-up
- Death

3.14 DATA AND SAFETY MONITORING

This study will be monitored in accordance with the sponsor's pharmacovigilance procedures. AEs and SAEs will be reviewed as part of ongoing safety surveillance. The sponsor will contact the investigators and applicable site staff regularly 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, in Part 1, mandatory safety teleconferences will occur before enrollment of subjects into the next cohort. In Part 2, teleconferences with investigators and applicable site staff will be conducted, or written communications sent, 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) on an as needed basis.

4.0 STUDY ACTIVITIES AND ASSESSMENTS

The schedule of events is provided in Appendix 5. Descriptions of the scheduled evaluations are outlined below and complete information on study drug and dosing is provided in Section 3.5.

Before study entry, throughout the study, and at the follow-up evaluation, various clinical and diagnostic laboratory evaluations are required. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated.

4.1 DESCRIPTION OF PROCEDURES

4.1.1 Informed Consent

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

4.1.2 Medical History

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

4.1.3 Adverse Events

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

4.1.4 Concomitant Medications and Therapy

Document all concomitant medications and procedures from within 21 days before the start of study drug administration through 30 days after the last dose of study drug.

4.1.5 Confirmation of Eligibility

Subject eligibility for enrollment will be assessed per Section 3.3. All screening procedures, unless otherwise indicated, should be completed within 21 days of the first dose of study drug.

4.1.6 ECOG Performance Status

The ECOG performance index is provided in Advani RH, Buggy JJ, Sharman JP, et al. Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. J Clin Oncol 2012;31:88-94.

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Appendix 1.

4.1.7 Physical Examination, Vital Signs, Height, & Weight

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 SFU visits.

For all subjects except those with MM, the following B symptoms will be collected at each examination:

- Unintentional weight loss of normal body weight over a period of ≤6 months
- Disease associated intermittent fevers ≥38 °C
- Drenching sweats especially at night

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

4.1.8 Bone Marrow Aspirate and Biopsy

A bone marrow aspirate and biopsy will be done at screening or up to 60 days before the first dose of study drug. Per the current response criteria (Bladé et al. 1998; Durie et al. 2006; Hallek et al. 2008; Owen et al. 2013; and Cheson et al. 2014), a bone marrow aspirate/biopsy will also be required at any time on study to confirm a complete response (CR). A bone marrow aspirate and biopsy will also be done at end of Cycle 12, and as clinically indicated. For subjects continuing study treatment beyond Cycle 12, bone marrow aspirate and biopsy to be done at investigator discretion, per standard of care. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's Form Food and Drug Administration (FDA) 1572. De-identified copies of all bone marrow biopsy/aspirate results may be requested by the sponsor.

When available, any unused bone marrow tissue will be used for exploratory correlative studies (Section 4.1.20). Correlative studies on bone marrow tissue will be done by the sponsor. Refer to the laboratory manual for sample handling and shipment instructions.

4.1.9 Electrocardiogram

A centralized cardiac safety monitoring laboratory will be used in this study to assess the potential of acalabrutinib and ACP-319 as evaluated by ECG measurement of the QTc interval.

Toxicity grading of QTc interval prolongation will be defined by CTCAE and provided in Table 4-1.

Table 4-1. QTc Toxicity Grading Defined by CTCAE

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

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram.

The service provider will provide the ECG equipment (12-lead surface), instructions, and training (when requested). Subjects should be in supine position and resting for ≥10 minutes before study-related ECGs. At screening, results from the central ECG reader (triplicates taken at least 1 minute apart) will be averaged to determine eligibility and must meet the eligibility criteria of QTc ≤480 ms. Thereafter, single ECGs are done at each timepoint (Table 4-2). However, if a machine-read ECG registers a QTc (either Bazett's or Fridericia'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 according to the machine on site (i.e., the subject has 2 consecutive ECGs taken ≥5 minutes apart with a QTc that is ≥501 ms, demonstrate a >60-ms change from baseline, or show other ventricular dysrhythmias per Table 4-1), ACP-319 must be held pending acquisition of the QTc results from the centralized review. If centralized review confirms both ECG QTc readings are ≥501 ms, show a >60 ms change from baseline, or show other ventricular dysrhythmias per Table 4-1, then the subject should have the ACP-319 held until those abnormalities resolve to baseline values and receive any further ACP-319 at a reduced dose level. Conversely, if the centralized review shows that both ECG QTc readings are ≤500 ms and the change in QTc is ≤60 ms from baseline, dosing may be restarted at the same dose level, but missed doses will not be made up.

Table 4-2. ECG Acquisition Times

Study Segment	Day	ECG Acquisition Times
Screening	--	Triplicate at least 1 min apart
Cycle 1	1	Single ECG predose, and 1, 2, 4, and 6 hours after 1st dose; window for ECGs at 1, 2, 4, 6 hours is ±10 minutes.
Cycle 1	8	Single ECG predose, and 1, 2, 4, and 6 hours after dose; window for ECGs at 1, 2, 4, 6 hours is ±10 minutes
Cycle 1	15, 22, 28	Single ECG 1 hour (±10 minutes) postdose
Cycle 2	15, 28	Single ECG anytime during the visit
Cycles 3 to 6	28	Single ECG anytime during the visit
Cycles 9 and 12	28	Single ECG anytime during the visit

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events;
ECG = electrocardiogram.
All timepoints relative to the morning dose.

4.1.10 Pregnancy Test

Urine or serum pregnancy tests will be required only for WOCBP. Testing will be done by a local or central laboratory as listed on the investigator's Form FDA 1572.

4.1.11 Hematology

Hematology studies must include complete blood count (CBC) with differential, including but not limited to white blood cell count, hemoglobin, hematocrit, platelet count, ANC, and absolute lymphocyte count (ALC). Testing will be done by a local or central laboratory as listed on the investigator's Form FDA 1572. Cycle 1 Day 1 hematology does not need to be repeated if screening hematology was done within 5 days.

4.1.12 Serum Chemistry

Chemistry will include albumin, ALP, ALT, AST, bicarbonate, blood urea nitrogen, bone-specific ALP, calcium, chloride, creatinine, C-terminal telopeptide, 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 done by a local or central laboratory as listed on

the investigator's Form FDA 1572. Cycle 1 Day 1 serum chemistry does not need to be repeated if screening chemistry was within 5 days.

4.1.13 Hepatitis B and C Testing

Hepatitis serology testing must include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody, anti-HBc, and hepatitis C virus (HCV) antibody. In addition, subjects testing positive for anti-HBc or HCV antibody must have respective PCR testing performed during screening (see Appendix 6 and exclusion criterion #12). Testing will be performed by local or central laboratory.

Subjects who are anti-HBc positive should have quantitative PCR testing for HBV DNA performed during screening and monthly thereafter. Monthly monitoring should continue until 12 months after last dose of study drug(s) for those on combination therapy and every 3 months for those on acalabrutinib monotherapy. Any subject with a rising viral load (above lower limit of detection) should discontinue study drug and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B. Since IVIG may cause false positive hepatitis serology, monthly PCR testing is not required in subjects who are currently receiving or received prophylactic IVIG within 3 months before study enrollment and have a documented negative anti-HBc test before the initiation of IVIG therapy. PCR testing should be performed when clinically indicated (e.g., in the setting of rising transaminase levels).

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

Refer to Section 3.11.1, and Appendix 6 regarding monitoring of subjects who are anti-HBc positive or hepatitis C antibody positive or who have a known history of HBV or hepatitis C.

4.1.14 Amylase and Lipase

Serum amylase and serum lipase testing will be done by a local or central laboratory as listed on the investigator's Form FDA 1572.

4.1.15 Urinalysis

Urinalysis includes pH, ketones, specific gravity, bilirubin, N-terminal telopeptide, protein, blood, and glucose. Testing will be done by a local or central laboratory as listed on the investigator's Form FDA 1572.

4.1.16 T/B/Natural Killer Cell Count

Flow cytometry testing will include $CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, and $CD16/56^+$ cells. Testing will be done by a local or central laboratory as listed on the investigator's Form FDA 1572.

4.1.17 Serum Immunoglobulin

Testing for IgG, IgM, and IgA will be done by a local or central laboratory as listed on the investigator's Form FDA 1572.

4.1.18 Disease Markers

MM Subjects:

Testing for serum M-protein levels (by serum protein electrophoresis [SPEP] and serum immunofixation electrophoresis [SIFE]), serum-free light chains (SFLC), urine M-protein levels (by urine serum protein electrophoresis [UPEP] and urine immunofixation electrophoresis [UIFE]), and serum β2-microglobulin will be done by a local or central laboratory as listed on the investigator's Form FDA 1572.

WM Subjects:

Serum M-protein levels (by SPEP and IFE) will be done by a local or central laboratory as listed on the investigator's Form FDA 1572.

4.1.19 Skeletal Survey for MM Subjects

Standard lateral radiograph of the skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femur, and humerus are required at screening or baseline (i.e., before the first dose of study drug), at Cycle 12, and as clinically indicated. Radiographic imaging and analysis will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's Form FDA 1572.

4.1.20 Pharmacodynamics and Correlative Studies

Blood samples will be used for PD testing (e.g., BTK occupancy and B-cell activation), cytokine analysis, and for further characterization of circulating lymphocyte and myeloid cell subsets.

CCI

CCI

Refer to the laboratory manual for instructions on collecting and shipment of the PD samples. All testing will be done by the sponsor or designee. CCI

4.1.21 Pharmacokinetics

Refer to the laboratory manual for instructions on collecting and processing these samples. Testing will be performed at a central clinical laboratory. Leftover plasma samples may be used for exploratory acalabrutinib and ACP-319 metabolite analyses, or assessment of free (unbound) plasma concentrations of ACP-319 and M20 and/or measurement of plasma concentrations of α1-acid glycoprotein. PK testing will be done for all subjects in Part 1 and for up to 24 subjects in Part 2 of the study as follows (Table 4-3).

Table 4-3. Pharmacokinetic Sample Schedule

Day	Pharmacokinetic Timepoints
Cycle 1: Day 1, 28	Up to 30 minutes before dosing and 0.5, 0.75, 1, 2, 4, and 6 hours after the morning dose of Day 1 and 28. Note the windows for these pharmacokinetic timepoints are ± 5 minutes.
Cycle 1: Day 8, 15, 22	Up to 30 minutes before and 1 hour (± 5 minutes) after the morning dose on these days
Cycle 2: Day 15, 28	Up to 30 minutes before the morning dose on these days
Cycles 3-4: Day 28	Up to 30 minutes before the morning dose on these days

All PK samples will be drawn relative to the morning dose.

4.1.22 Tumor Assessments

DLBCL (non-GCB and GCB), MCL, FL, CLL/SLL, RS, and WM:

A pretreatment CT scan with contrast (unless contraindicated) is required of the chest, abdomen, and pelvis and any other disease sites (e.g., neck) within 30 days before the first dose of study drug. A pretreatment positron-emission topography (PET)/CT scan is optional; however, if a recent PET/CT scan (within 90 days of the first dose) is available, the information will be recorded. Information on extranodal involvement will also be recorded.

For subjects with baseline (screening) extramedullary disease, on-treatment CT scans with contrast (unless contraindicated) of the chest, abdomen, and pelvis and any other disease sites (e.g., neck) will be done for tumor assessments at the end of Cycle 2 (±7 days), Cycle 4 (±7 days), and Cycle 6 (±7 days); every 3 cycles (12 weeks, ±7 days) through Cycle 18, and then every 6 cycles thereafter, or more frequently at investigator discretion. A CT scan is also done at the TT visit, if not done at the time of disease progression. Depending on the tumor type (eg MM, B-ALL, or WM in the absence of baseline extramedullary disease), on-study tumor assessments may be done by laboratory studies. Bone marrow and PET/CT are required for confirmation of CR per clinical guidelines (see Section 4.2).

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

In the event disease progression is suspected due to physical examination or laboratory test, a CT and/or PET/CT scan must be performed to confirm disease progression. There must be radiographically measurable disease at screening (≥1 lymph node >2.0 cm in the longest diameter). If the sole lesion lies within the field of prior radiotherapy, there must be evidence of disease progression in that lesion.

Up to 6 measurable lymph nodes (only target lesions >1.5 cm in the longest diameter may be assessed), clearly measurable in 2 perpendicular dimensions, will be followed as target lesions for each subject. Measurable sites of disease should be chosen such that they are representative of the subject's disease. In addition, selection of target lesions should be from as disparate regions of the body as possible when these areas are significantly involved. If additional lesions are present but are not included in the target lesion assessment, they can be added as non-target lesions followed throughout the study. The cranial-caudal measurement of the spleen and longest diameter of the liver will be assessed at screening and all subsequent response evaluations.

MM

Baseline myeloma assessments will consist of:

- M-protein determination using the following procedures:
  - SPEP and SIFE
  - UPEP and UIFE (all using the same 24-hour urine collection)
- SFLC
- Plasmacytoma evaluation
- Bone marrow to quantify percent myeloma cell involvement (aspirate and biopsy required at baseline)
- Skeletal survey: lateral radiograph of the skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri
- β2-microglobulin

On-study myeloma assessments will consist of:

- SPEP and/or UPEP (if results were measurable at baseline); quantitative immunoglobulins if used to follow disease; immunofixation to confirm a CR
- SFLC
- Plasmacytoma evaluation (if only measurable disease at baseline)
- Bone marrow aspirate and/or trephine bone biopsy (to confirm a CR or if clinically indicated).

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

4.1.23 Routine Clinical Assessments

Routine clinical assessments include physical examinations, recording of symptoms, and hematologic evaluations to evaluate for both AEs and assessment of disease progression at times when the CT and/or PET/CT scan is not obtained. The investigator should report any suspected disease progression to the sponsor or designee via the electronic data capture (EDC) system within 24 hours of discovery.

4.1.24 CMV Testing

For subjects receiving ACP-319, CMV testing at screening must include serology testing for CMV IgG, CMV IgM, and CMV PCR testing. Subjects receiving ACP-319 must have monthly CMV serology and PCR testing. Monthly laboratory testing should continue until 12 months after last dose of ACP-319. Testing will be done by a local or central laboratory.

4.1.25 Study Drug Accountability

See Section 7.7.

4.2 INVESTIGATOR'S ASSESSMENT OF RESPONSE TO TREATMENT

The investigator must rate the response of the subject's non-Hodgkin lymphoma (NHL) or RS, CLL/SLL, WM, B-ALL, or MM as outlined below:

- NHL or RS refer to Table 4-4
- CLL/SLL refer to Table 4-5
- WM refer to Table 4-6
- B-ALL refer to Table 4-7
- MM refer to Table 4-8

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

Note: Transient worsening of disease during temporary interruption of study therapy (e.g., for drug-related toxicity, surgery, or intercurrent illness) may not indicate disease progression. In such circumstances, and if medically appropriate, subjects may resume therapy and relevant clinical, laboratory, and/or radiographic

assessments should be done to document whether tumor control can be maintained or whether actual disease progression has occurred.

Table 4-4. Response Assessment Criteria for NHL

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

Footnotes appear after the last page of the table.

Table 4-4. Response Assessment Criteria for NHL (continued)

Response and Site	PET-CT-Based Response	CT-Based Response
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	<50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi >1.5 cm and Increase by ≥50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤2 cm 1.0 cm for lesions >2 cm In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

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

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

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

Table 4-5. Response Assessment Criteria for CLL

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	Normal (e.g., no lymph nodes >1.5 cm)	Persistent anemia, thrombocytopenia, or neutropenia related to drug toxicity
nPR	CR with the presence of lymphoid nodules in the bone marrow which reflect residual disease.			
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	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]

Table 4-5. Response Assessment Criteria for CLL

Response	Lymphocytes	Bone Marrow	Physical Examination[a] (Nodes, Liver, Spleen)	Peripheral Blood
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 Hemoglobin decrease of >2 g/dL from baseline secondary to CLL

Modified from Hallek et al. 2008.
Abbreviations: ANC = absolute neutrophil count; CLL= chronic lymphocytic leukemia; CR = complete response; CRi = CR with incomplete blood count recovery; nPR = nodular partial remission; PD = progressive disease; PR = partial remission (response); PRL = partial remission (response) with treatment-induced lymphocytosis; SD = stable disease.
*CR: all of the above CR criteria have to be met, and patients 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 ≥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 et al. 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. In 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 4-6. Response Assessment Criteria for WM

Response	Definition
Complete response (CR)	Absence of serum monoclonal IgM protein by immunofixation Normal serum IgM level Complete resolution of extramedullary disease, i.e., lymphadenopathy and splenomegaly if present at baseline Morphologically normal bone marrow aspirate and trephine biopsy
Very good partial response (VGPR)	Monoclonal IgM protein is detectable ≥90% reduction in serum IgM level from baseline[a] Complete resolution of extramedullary disease i.e., lymphadenopathy/splenomegaly if present at baseline No new signs or symptoms of active disease
Partial response (PR)	Monoclonal IgM protein is detectable ≥50% but < 90% reduction in serum monoclonal IgM level from baseline[a] Reduction in extramedullary disease i.e., lymphadenopathy/splenomegaly if present at baseline No new signs or symptoms of active disease
Minor response (MR)	Monoclonal IgM protein is detectable ≥25% but <50% reduction in serum monoclonal IgM level from baseline[a] No new signs or symptoms of active disease
Stable disease (SD)	Monoclonal IgM protein is detectable <25% reduction and <25% increase in serum monoclonal IgM level from baseline[a] No progression in extramedullary disease i.e., lymphadenopathy/splenomegaly No new signs or symptoms of active disease
Progressive disease (PD)	≥25% increase in serum IgM level[a] from lowest nadir (requires confirmation on ≥2 consecutive measurements at least 4 weeks apart). AND Progression of clinical features attributable to the disease per Owen et al. 2013 and Cheson et al. 2014.

Owen et al. 2013, Cheson et al. 2014
Abbreviations: CR = complete response; Ig = immunoglobulin; MR = minor response; PD = progressive disease; PR = partial response; SD = stable disease; VGPR = very good partial response; WM = Waldenström macroglobulinemia.
a. Sequential changes in IgM levels may be determined either by M protein quantitation or total serum IgM quantitation by nephelometry.

Table 4-7. Response Assessment Criteria for B-ALL

Response	Definition
Complete response (CR)	□ No circulating blasts or extramedullary disease □ Trilineage hematopoiesis and <5% blasts □ ANC >1000/μL □ Platelets >100,000/μL □ No recurrence for 4 weeks
CR with incomplete blood count recovery (CRi)	□ Recovery of platelets but <100,000/μL or ANC <1000/μL
Progressive disease	□ Increase of at least 25% in the absolute number of circulating or bone marrow blasts or development of extramedullary disease

Abbreviations: ANC = absolute neutrophil count; B-ALL = B-cell acute lymphoblastic leukemia; CR = complete response; CRi = complete response with incomplete blood count recovery.

Table 4-8. Response Criteria for MM (incorporating EBMT and IMWG)

Response Subcategory	Response Criteria[a]
Complete response (CR)	Negative immunofixation on the serum and urine and Disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow[b]
Stringent complete response (sCR)	CR as defined above plus Normal FLC ratio and Absence of clonal cells in bone marrow[b] by immunohistochemistry or immunofluorescence[c]
Near complete response (nCR)	Meeting the criteria for CR, except that the persistence of original monoclonal protein by immunofixation while absence of monoclonal protein on serum or urine protein electrophoresis
Very good partial response (VGPR)	Serum and urine M-component detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-component plus urine M-component <100 mg per 24 h
Partial response (PR)	≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥90% or to <200 mg per 24 h If the serum and urine M-protein are unmeasurable at baseline, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein are unmeasurable at baseline, and serum free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required.
Minor response (MR)	MR includes subjects in whom some, but not all, criteria for PR are fulfilled providing the remaining criteria satisfy the requirements for MR. Requires all of the following: o ≥25% to ≤9% reduction in the level of serum monoclonal protein for ≥2 determinations 6 weeks apart o If present, a 50% to 89% reduction in 24-h light chain excretion, which still exceeds 200 mg/24 h, for ≥2 determinations 6 weeks apart o 25-49% reduction in the size of plasmacytomas (by clinical or radiographic examination) for ≥6 weeks o No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)

Table 4-8. Response Criteria for MM (incorporating EBMT and IMWG)

Response Subcategory	**Response Criteria[a]**
Stable disease (SD) (not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates)	□ Not meeting criteria for CR, VGPR, MR, PR, or progressive disease.
Progression Subcategory	**Progression Criteria[d]**
Progressive disease[a] — To be used for calculation of duration of response and progression-free survival end points for all subjects including those in CR (includes primary progressive disease and disease progression on or off therapy)[g]	Laboratory or biochemical relapse or progressive disease: requires the occurrence of ≥1 of any of the following: □ Increase of ≥25% from lowest response value in serum M-component and/or (the absolute increase must be ≥0.5 g/dL)[e] □ Urine M-component and/or (the absolute increase must be ≥200mg/24 h) □ Only in subjects without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be >10 mg/dL □ Bone marrow plasma cell percentage: the absolute % must be ≥10%[f] □ Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas.

EBMT (Bladé et al. 1998) and IMWG (Durie et al. 2006)

Abbreviations: CR = complete response; EBMT = European Group for Blood and Marrow Transplant; FLC = (serum) free light chains; IMWG = International Myeloma Working Group; MM = multiple myeloma; MR = minor response; nCR = near complete response; PR = partial response; sCR = stringent complete response; SD = stable disease; VGPR = very good partial response.

Note clarification to IMWG criteria for coding CR and VGPR in subjects in whom the only measurable disease is by serum FLC levels: CR in such subjects a normal FLC ratio of 0.26-1.65 in addition to CR criteria listed above. VGPR in such subjects is defined as a >90% decrease in the difference between involved and uninvolved free light chain FLC levels.

a. All response categories require 2 consecutive assessments made at ≥4 weeks after the start of study therapy and any time before the institution of any new therapy after study therapy; CR and PR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.
b. Confirmation with repeat bone marrow biopsy not needed.
c. Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry and/or immunofluorescence requires a

minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is kappa/lambda of >4:1 or <1:2.

d. All relapse categories require 2 consecutive assessments made at any time before classification as relapse or disease progression and/or the institution of any new therapy.
e. For progressive disease, serum M-component increases of ≥1 gm/dL are sufficient to define relapse if starting M-component is ≥5 g/dL.
f. Relapse from CR has the 5% cutoff versus 10% for other categories of relapse.
g. For purposes of calculating time to progression and progression-free survival, CR subjects should also be evaluated using criteria listed above for progressive disease.

4.3 TT AND SFU VISITS

A TT visit is required for safety assessments for any subjects who permanently discontinue study treatment early for any reason including disease progression. The TT visit should be scheduled within 7 days of the last dose of study dose, if possible, and is not required for subjects who discontinue from the study within 10 days of a scheduled study visit.

Each subject should be followed until the SFU visit at 30 (+7) days after his or her last dose of study drug to monitor for resolution or progression of AEs (see Section 6.3.6) and to document the occurrence of any new events, regardless of whether the subject receives a new anticancer therapy or demonstrates disease progression within this timeframe. Subjects should bring any remaining capsules to the clinic at the SFU visit. Subjects who withdraw consent for study treatment should still be encouraged to complete the SFU assessments, but these assessments cannot be mandated if subject consent for further study participation is withdrawn. If the TT visit and the SFU visit coincide, then these can be combined into 1 visit. The schedule of assessments (Appendix 5) describes the procedures required for the TT and SFU visits.

4.4 DISCONTINUATION FOLLOW-UP FOR PROGRESSION AND TIME-TO NEXT TREATMENT

Each subject should be followed until disease progression or the start of alternative anticancer therapy. If neither of these has occurred at the time of the 30-day SFU visit, DFU visits should occur approximately every 3 months until disease progression or next anticancer treatment. During this period, subjects will be followed via CBC, and CT scans per investigator discretion. Refer to Appendix 5 for the full list of assessments required during this period.

4.5 MISSED EVALUATIONS

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

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

5.0 STATISTICAL METHODS OF ANALYSIS

5.1 GENERAL CONSIDERATIONS

Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions and confidence intervals (Cis) for discrete variables) will be used to summarize data as appropriate. As appropriate, analyses will be performed by dosing cohort, cancer type, or overall. Depending on dose escalation into subsequent cohorts and potential expansion cohorts, up to 108 evaluable subjects will be enrolled in this study.

In Part 1 (dose-escalation portion), enrollment of 6 subjects per cohort of the study limits the total cohort size consistent with the expected safety profiles of the study drugs but includes sufficient subjects per cohort to explore dose-dependent effects on PD biomarkers of BTK and PI3Kδ inhibition. The study employs the standard National Cancer Institute definition of MTD (starting dose associated with Cycle 1 DLT in <33.3% of subjects). The cohort size and dose-escalation rules establish a low probability of increasing the dose if the true rate of DLT is high while there is a high likelihood of escalating or proceeding to the next stage of the study if the true underlying proportion of DLT is low.

In Part 2 (expansion groups), enrollment of up to 12 subjects per histology offers the opportunity to determine if there is sufficient antitumor activity to warrant further development in the selected tumor types. Considering the planned expansion cohort size of 12 subjects, Table 5-1 shows the 2-sided exact 90% binomial CIs on the true response rate for the range of all possible values for the observed response rate.

Table 5-1. Two-Sided Exact 90% CIs for ORR in Expansion Cohorts (N=12)

Responses, n	Response Rate, %	90% Exact Binomial CI	
		Lower Bound	Upper Bound
0	0%	0%	22%
1	8%	0%	34%
2	17%	3%	44%
3	25%	7%	53%
4	33%	12%	61%
5	42%	18%	68%
6	50%	25%	75%
7	58%	32%	82%
8	67%	39%	88%
9	75%	47%	93%
10	83%	56%	97%
11	92%	66%	100%
12	100%	78%	100%

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

5.2 DEFINITION OF ANALYSIS POPULATIONS

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

- **All-treated population:** All enrolled subjects who receive ≥1 dose of study drug. The safety analyses and primary efficacy analyses will be performed on the All-treated population.
- **Efficacy-evaluable population:** All subjects in the All-treated population who have ≥1 evaluable response assessment after the first dose of study drug. Sensitivity analyses for efficacy will be carried out on the Efficacy-evaluable population.

5.3 MISSING DATA HANDLING

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

Duration of Response and Progression-free Survival: Data for subjects without disease progression or death will be censored at the date of the last tumor assessment and before the initiation of alternative anticancer therapy.

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

5.4 ENDPOINT DATA ANALYSIS

5.4.1 Safety Endpoint

Safety summaries will include summaries in the form of tables and listings. The frequency (number and percentage) of treatment emergent AEs will be reported in each treatment group by MedDRA System Organ Class and Preferred Term. Summaries will

also be presented by the severity of the AE (per CTCAE, v4.03 or higher, and by relationship to study drug (e.g., either acalabrutinib, ACP-319, or both).

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

Results of vital sign assessments, ECGs, and physical examinations will be tabulated and summarized.

5.4.2 Demographics and Baseline Characteristics

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

5.4.3 Study Treatment Administration

Descriptive information will be provided regarding the duration of study treatment exposure, average daily dose, and relative dose intensity.

For each subject, acalabrutinib relative dose intensity will be described in terms of the proportion of study drug actually taken relative to the amount that was planned during the treatment exposure period.

Descriptive information will be provided regarding the duration of study treatment exposure, average daily dose, and relative dose intensity.

For each subject, acalabrutinib and ACP-319 relative dose intensity will be described in terms of the proportion of study drug actually taken relative to the amount that was planned during the treatment exposure period.

5.4.4 Analysis of Efficacy Parameters

Response Rate

The primary efficacy endpoint is the ORR as assessed by investigators. ORR is defined as the proportion of subjects who achieve a response (see Table 4-4, Table 4-5, Table 4-6, Table 4-7, and Table 4-8). ORR will be calculated and the corresponding 2-sided 95% CI will be derived.

In addition, for subjects with CLL/SLL, response will be assessed according to Table 4-5, which reflects modified International Working Group response criteria (Hallek et al. 2008)

as recently updated (Cheson et al. 2012) to include partial remission (response) with treatment-induced lymphocytosis (PRL). For purposes of this analysis, lymphocytosis at a given timepoint will be defined as ALC, which is above normal limits and is not ≥50% decreased from baseline.

Duration of Response

The duration of response defined as the interval from the first documentation of response to the earlier of the first documentation of definitive disease progression or death from any cause. Kaplan-Meier methods will be used to estimate event-free curves and corresponding quantiles (including the median). Data from surviving, non-progressing subjects will be censored at the earliest of the time of initiation of anticancer treatment other than the study treatment or the last time that lack of disease progression was objectively documented. Data from subjects who have disease progression or die after ≥2 consecutive missing tumor assessments will be censored at the last time before the missing assessments that lack of disease progression was objectively documented.

Progression-Free Survival

Progression-free survival is defined as the interval from the start of acalabrutinib and ACP-319 therapy to the earlier of the first documentation of objective disease progression or death from any cause. Kaplan-Meier methods will be used to estimate the event-free curves and corresponding quantiles (including the median). Data from surviving, non-progressing subjects will be censored at the earliest of the time of initiation of anticancer treatment other than the study treatment or the last time that lack of disease progression was objectively documented. Data from subjects who have disease progression or die after ≥2 consecutive missing tumor assessments will be censored at the last time prior to the missing assessments that lack of disease progression was objectively documented.

Time-to-Next Treatment

Time-to-next treatment defined as the time from start of acalabrutinib and ACP-319 therapy on this protocol to the start of the next treatment. Kaplan-Meier methods will be used to estimate the event-free curves and corresponding quantiles (including the median). Data from subjects who have not received subsequent therapy will be censored at the earliest of death or the last time that lack of administration of a new therapy was objectively documented.

5.4.5 Analysis of Pharmacokinetic/Pharmacodynamic Parameters

The plasma pharmacokinetics of acalabrutinib and ACP-319 and a metabolite (M20) of ACP-319 will be characterized using noncompartmental analysis. The following PK parameters will be calculated, whenever possible, from plasma concentrations of analytes:

- $AUC_{0\text{-}last}$ Area under the plasma concentration-time curve calculated using trapezoidal summation from time 0 to time last, where "last" is the time of the last measurable concentration (C_t)
- $AUC_{0\text{-}12}$ Area under the plasma concentration-time curve from 0 to 12 hours, calculated using trapezoidal summation
- $AUC_{0\text{-}inf}$ Area under the plasma concentration-time curve from 0 to infinity, calculated using the formula: $AUC_{0\text{-}inf} = AUC_{0\text{-}last} + C_{last} / \lambda_z$, where λ_z is the apparent terminal elimination rate constant
- $AUC_{0\text{-}24calc}$ Area under the plasma concentration-time curve from 0 to 24 hours, calculated by doubling the value for $AUC_{0\text{-}12}$
- C_{max} Maximum observed plasma concentration
- T_{max} Time of the maximum plasma concentration (obtained without interpolation)
- $t_{½}$ Terminal elimination half-life (whenever possible)
- λ_z Terminal elimination rate constant (whenever possible)
- CL/F Oral clearance
- Vz/F: Oral volume of distribution

Missing dates or times may be imputed for PK and PD samples if the missing values can be established with an acceptable level of accuracy based on other information obtained during the visit in question. Steady state predose drug concentrations may be used to estimate the subsequent trough (12 hour) concentration when 12-hour concentration data are not available. If PK and PD sampling for a given subject is not performed according to protocol instructions, that subject may be excluded from the PK and PD analyses.

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

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

5.4.6 Explorative or Correlative Analyses

CCI

6.0 ASSESSMENT OF SAFETY

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

6.1 REFERENCE SAFETY INFORMATION

For the purpose of reporting AEs and SAEs, the Investigator Brochure for acalabrutinib contains the Reference Safety Information (RSI).

6.2 DEFINITIONS

6.2.1 Adverse Events

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

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 the primary hematologic malignancy that were not present before the AE reporting period (see Section 6.3.1).

- Preexisting 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).

6.2.2 Serious Adverse Event

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

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

- It results in death (i.e., the AE actually causes or leads to death).

- It is life-threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. 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 investigational product.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

6.2.3 Severity

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

- Grade 1 (Mild AE) – experiences 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 activities, 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

6.2.4 Adverse Events of Special Interest

The following are adverse events of special interest (specific to acalabrutinib) and must be reported to the sponsor expeditiously (see Section 6.3.5 for reporting instructions), irrespective of regulatory seriousness criteria or causality:

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

6.3 DOCUMENTING AND REPORTING OF ADVERSE AND SERIOUS ADVERSE EVENTS

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, as outlined in the prior sections, are recorded on the CRF. If

electronic SAE reporting is not available, a paper SAE form must be emailed or faxed to Acerta Pharma Drug Safety, or designee (see Section 6.3.5).

6.3.1 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 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 until the subject is lost to follow-up or withdraws consent. Resolution/stable means the subject has returned to baseline state of health or the investigator does not expect any further improvement or worsening of the event.

6.3.2 Assessment of Adverse Events

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

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

Each recorded AE or SAE will be described by its diagnostic term, duration (e.g., start and end dates), severity, regulatory seriousness criteria, if applicable, suspected relationship to the study drugs (see following guidance), and any actions taken. The causality of AEs to the study drugs will be assessed by means of the question: 'Is there a reasonable possibility that the event may have been caused by the study drugs?' per FDA guidance on safety reporting requirements (Food and Drug Administration. Guidance for Industry and Investigators. Safety reporting requirements for INDs and BA/BE Studies. 2012 Dec).

See Appendix 4 for more detail on assessing causality.

6.3.3 Malignant Tumors

Adverse events for malignant tumors reported during the study should generally be assessed as SAEs. If no other seriousness criteria apply, the "Important Medical Event" criterion should be used. In certain situations; however, medical judgement 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 State 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 which entry into the study is a criterion and that is being treated by the investigational product under study and is not the development of new or progression of existing metastasis to the tumor under study). Malignant tumors that—as part of normal, if rare, progression—undergo transformation (e.g., Richter's transformation of B cell CLL into diffuse large B-cell lymphoma) should not be considered a new malignant tumor.

6.3.4 Pregnancy

The investigator should report all pregnancies and pregnancies in the partners of subjects within 24 hours using the Pregnancy Report Form. This form should be faxed or emailed to Acerta Pharma Drug Safety. Any pregnancy-associated SAE must be reported using the SAE form, according to the usual timelines and directions for SAE reporting (Section 6.3.5).

Any uncomplicated pregnancy that occurs with the subject or with the partner of a treated subject during this study will be reported for tracking purposes only, if agreed to by the subject or the partner of the subject in this study. All pregnancies and partner pregnancies that are identified during or after this study, wherein the estimated date of conception is determined to have occurred from the time of consent to 2 days after the last dose of acalabrutinib and 90 days after the last dose of ACP-319, will be reported,

followed to conclusion, and the outcome reported, as long as the subject or partner has consented to participate in follow-up. Pregnancy itself is not regarded as an AE unless there is suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Likewise, elective abortions without complications are not considered AEs. Any SAEs associated with pregnancy (e.g., congenital abnormalities/birth defects/spontaneous miscarriages or any other serious events) must additionally be reported as such using the SAE form.

Subjects should be instructed to immediately notify the investigator of any pregnancies. Any female subjects receiving acalabrutinib and/or ACP-319 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 PPD

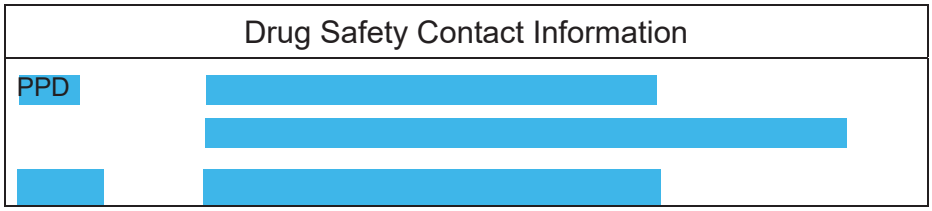
6.3.5 Expedited Reporting Requirements for Serious Adverse Events

All SAEs must be reported within 24 hours of discovery. All initial SAE reports and follow-up information will be reported using the protocol-specific EDC system. If electronic SAE reporting is not available, paper SAE forms must be completed and emailed or faxed to Acerta Pharma Drug Safety or designee. Acerta Pharma may request follow-up and other additional information from the investigator (e.g., hospital admission/discharge notes and laboratory results).

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

Death due to disease progression should be recorded on the appropriate form in the EDC 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 Acerta Pharma Drug Safety, or designee, as outlined above. If study drug is discontinued because of an SAE, this information must be included in the SAE report.

An SAE may qualify for mandatory expedited reporting to regulatory authorities if the SAE is attributable to the investigational product (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 acalabrutinib Investigator Brochure (i.e., an unexpected event). In this case, Acerta Pharma Drug Safety/Designee will forward a formal notification describing the suspected unexpected serious adverse reaction (SUSAR) to all investigators. Each investigator must then notify his or her IRB/ IEC of the SUSAR.



6.3.6 Type and Duration of Follow-Up of Subjects after Adverse Events

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

7.0 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 include:

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

7.1 REGULATORY AND ETHICAL COMPLIANCE

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

7.2 INSTITUTIONAL REVIEW BOARD AND INDEPENDENT ETHICS COMMITTEE

The investigator will submit this protocol, the ICF, Investigator Brochure, and any other relevant supporting information (e.g., all advertising materials) to the appropriate IRB/IEC for review and approval before study initiation. A signed protocol approval page; a letter confirming IRB/IEC approval of the protocol and ICF; and a statement that the IRB/IEC is organized and operates according to 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 Form FDA 1572 (Statement of Investigator Form) to Acerta Pharma before screening subjects for study enrollment. Amendments to the protocol must also be approved by the IRB/IEC and local regulatory agencies, as appropriate, before the implementation of changes in this study.

7.3 INFORMED CONSENT AND PROTECTED SUBJECT HEALTH INFORMATION AUTHORIZATION

A copy of the IRB/IEC-approved ICF must be forwarded to 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 § 21 CFR Part 50, and other applicable national and local regulations governing ICF. Each subject must provide a signed and dated ICF before enrollment into this study. If allowed by the protocol, a legal representative may sign the ICF for a subject incapable of giving consent. Signed consent forms must remain in each subject's study file and be available for verification by study monitors at any time.

In accordance with individual local and national patient privacy regulations, the investigator or designee **must** explain to each subject that for the evaluation of study results, the subject's protected health information obtained during the study may be shared with Acerta Pharma and its designees, regulatory agencies, and IRBs/IECs. 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 (including those who did not undergo screening) 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 CRFs designed for this study according to the completion guidelines that will be provided within the clinical database. The investigator will ensure that the CRFs are accurate, complete, legible, and completed promptly. Refer to Section 7.8 for record retention requirements.

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 by the sponsor, regulatory authorities, or ethics committees.

Every effort will be made to maintain the anonymity and confidentiality of all subjects during this clinical study. However, because of the experimental nature of this treatment, the investigator agrees to allow the IRB/IEC, representatives of 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 and ACP-319 capsules must be kept in a locked limited access cabinet or space. The study drug must not be used outside the context of the protocol.

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

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

Contents of each shipment must be visually inspected to verify the quantity and document the condition of study drug capsules. The designated recipient completes and signs the CSSF. A copy of the signed CSSF must be faxed or emailed to Acerta Pharma at the fax number/email address listed on the form.

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

1. study identification number (ACE-LY-001)
2. subject identification number
3. lot number(s) of acalabrutinib and ACP-319 dispensed for that subject
4. date and quantity of drug dispensed
5. any unused drug returned by the subject

At study initiation, the monitor will evaluate and approve the site's procedure for investigational product disposal/destruction to ensure that it complies with 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 designee, for return of unused investigational product. Before disposal/destruction, final drug accountability and reconciliation must be performed by the monitor.

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

7.8 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 Form FDA 1572, IRB/IEC approval letters, signed ICFs, drug accountability records, SAE information transmitted to Acerta Pharma, subject files (source documentation) that substantiate entries in CRFs, 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 returned 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 will initiate any change to the protocol in a protocol amendment document. The amendment will be submitted to the IRB/IEC together with, if applicable, a revised model ICF. If the change in any way increases the risk to the subject or changes the scope of the study, then written documentation of IRB/IEC approval must be received by 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 study.

7.10 PUBLICATION OF STUDY RESULTS

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

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

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Appendix 1. Performance Status Scores

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about >50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair >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 2. Risk Factors for Drug-induced Torsades de Pointes

- History of congenital long QT syndrome
- Baseline QTc prolongation (>450 ms)
- Hypokalemia (potassium ≤3.0 mEq/L)
- Severe hypomagnesemia (magnesium ≤1.2 mEq/L)
- Bradycardia (resting heart rate <55 beats per minute)
- Current or recent past use (within 7 days before study entry) of drugs known to prolong QTc interval and may be associated with Torsades de Pointes (listed below):

  amiodarone, amitriptyline, arsenic, astemizole, bepridil, chloroquine, chlorpromazine, ciprofloxacin, cisapride, clarithromycin, desipramine, disopyramide, dofetilide, dolasetron, domperidone, doxepin, droperidol, erythromycin, fluoxetine, gatifloxacin, halofantrine, haloperidol, ibutilide, imipramine, indapamide, itraconazole, ketoconazole, levofloxacin, levomethadyl, mesoridazine, methadone, moxifloxacin, pentamidine, pimozide, probucol, procainamide, procainamide, quetiapine, quinidine, quinidine, risperidone, sertraline, sotalol, sparfloxacin, sumatriptan, terfenadine, thioridazine, venlafaxine, ziprasidone, zolmitriptan,

This list is not exhaustive and new information regarding drugs with dysrhythmic potential emerges on a regular basis. Please refer to the following site (or similar sites) for additional information on drugs with dysrhythmic potential:

http://www.credible meds.org.

Appendix 3. Examples of Coadministered Drugs That Need Additional Consideration

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

Strong Inhibitors of CYP3A	Moderate inhibitors of CYP3A
boceprevir	aprepitant
clarithromycin[a]	cimetidine
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.

After discontinuation of the strong or moderate 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		
iopinavir 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 4. Adverse Event Assessment of Causality

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

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 drugs.

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 drugs.

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 5. Schedule of Assessments – Acalabrutinib Monotherapy

	Cycles >12[a,b]	TT Visit[c]	Safety Follow- up Visit[c]	DFU[d]
	Every 3 months (± 7)	+ 7 days after last dose	30 days (+ 7) after last dose	Every 3 months
PE[e]/Vital signs[f]/Weight	x	X	x	
ECOG status	x	X	x	
Lab assessments:				
Pregnancy test[g]	x	X	x	
Hematology[h]	x	X	x	x
Serum chemistry[i]	x	X	x	
HBV PCR[j]	x			x
Amylase and lipase		X	x	
Urinalysis[k]				
T/B/NK cell count[l]	Every 6 months			
Serum Ig[m]	Every 6 months	X	x	
Disease markers[n] (MM and WM only)	Every 3 months	X	x	
Bone marrow (aspirate/biopsy)[o]	Investigator discretion & to confirm CR			
Skeletal survey (MM only)[p]	Investigator discretion			
Pharmacodynamics		X		
Acalabrutinib dispensed	x			
Study drug compliance	x			
Tumor assessment[o,p,q,r]	x	X	x	
Radiologic assessment[q]	Cycle 15, 18, then every 6 cycles	X		Investigator discretion
Concomitant medications	x	X	x	
Adverse events[s]	x	X	x	x
Time-to-next treatment			x	x

Abbreviations: AE = adverse event; ALC = absolute lymphocyte count; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; anti-HBc = hepatitis B core antibody; AST = aspartate aminotransferase; B-ALL = B-cell acute lymphoblastic leukemia; BUN = blood urea nitrogen; CBC = complete blood count; CR = complete response; CT = computed tomography; DFU = discontinuation follow-up; ECOG = Eastern Cooperative Oncology Group; HBV = hepatitis B virus; Ig = immunoglobulin; IVIG = intravenous immunoglobulins; LDH = lactate dehydrogenase; MM = multiple myeloma; NK = natural killer; PCR = polymerase chain reaction; PE = physical examination; PET = positron-emission tomography; SFU = safety follow-up; TT = treatment termination; WM = Waldenström macroglobulinemia.

Footnotes for ACE-LY-001 Schedule of Study Activities – Acalabrutinib monotherapy:

a. Subjects who have received 12 cycles of study treatment and who have discontinued ACP-319 for ≥3 cycles will follow study assessments as listed in the Schedule of Activities.
b. Any subjects who have not progressed while receiving study treatment may continue to receive acalabrutinib until the end of study, defined as 36 months after the last subject is enrolled. Subjects who are still on treatment at the end of the study and deriving clinical benefit from acalabrutinib monotherapy may be eligible to enroll in a rollover or safety extension study of acalabrutinib monotherapy (see Section 3.0).
c. A 30-day (+7 days) SFU visit is required when subjects discontinue study treatment. A TT visit is required for any subjects who permanently discontinue study treatment early for any reason including disease progression. The TT visit should be scheduled within 7 days of the last dose of study drug, if possible, and is not required for subjects who discontinue from the study within 10 days of a scheduled study visit. If the TT visit and the SFU visit coincide, then these can be combined into 1 visit. Subjects should bring any remaining capsules to the clinic at the SFU visit.
d. If disease progression or the start of alternative anticancer therapy has not occurred at the time of the 30-day SFU visit, DFU visits should occur approximately every 3 months until disease progression or next anticancer treatment.
e. Symptom-directed physical examinations will be performed. For all subjects except those with MM, the following B symptoms will be collected at each examination: unintentional weight loss of normal body weight over a period of ≤6 months; disease associated intermittent fevers ≥38°C; drenching sweats, especially at night.
f. Vital signs (blood pressure, heart rate, and body temperature) will be assessed after the subject has rested in the sitting position.
g. Urine or serum pregnancy test must be performed in women of childbearing potential only.
h. Hematology must include CBC with differential, including, but not limited to white blood cell count, hemoglobin, hematocrit, platelet count, ANC, and ALC.
i. Serum chemistry: albumin, ALP, ALT, AST, bicarbonate, BUN, bone-specific ALP, calcium, chloride, creatinine, C-terminal telopeptide, glucose, LDH, magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid.
j. Subjects who are anti-HBc positive (or have a known history of HBV infection) should have a monthly quantitative PCR test for HBV DNA. Monthly monitoring should continue until 12 months after last dose of study drug(s) for those on combination therapy and every 3 months for those on acalabrutinib monotherapy. Any subject with a rising viral load (above lower limit of detection) should discontinue study drug(s) and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B. As IVIG may cause false positive serology, monthly PCR testing is not required in subjects who are currently receiving or received prophylactic IVIG within 3 months prior to study enrollment and have a documented negative anti-HBc before the initiation of IVIG therapy, unless clinically indicated (e.g., in the setting of rising transaminase levels).
k. Urinalysis: pH, ketones, specific gravity, bilirubin, N-terminal telopeptide, protein, blood, and glucose.
l. T/B/NK cell count (i.e., CD3, CD4, CD8, CD19, CD16/56); done every 6 months.
m. Serum immunoglobulin: IgG, IgM, IgA; done every 6 months.
n. Refer to Section 4.1.18 for a list of MM and WM disease markers.
o. Bone marrow aspirate and biopsy to be done at investigator discretion, per standard of care. Bone marrow and PET/CT are only required for confirmation of CR per clinical guidelines (see Section 4.2). CCI .
p. Skeletal surveys for MM subjects are to be done at investigator discretion.
q. CT scans are not required for subjects with MM or B-ALL. For subjects with baseline (screening) extramedullary disease, on-treatment CT scans will be done for tumor assessments at Cycles 12, 15, and 18, and then every 6 cycles thereafter, or more frequently at the investigator's discretion. A CT scan is also done at the TT visit if not done at the time of disease progression. Bone marrow and PET/CT are only required for confirmation of CR per clinical guidelines (see Section 4.2). On-treatment radiologic tumor assessments are not required for subjects who do not have baseline extramedullary disease.
r. Depending on the tumor type (e.g., MM, B-ALL, or WM in the absence of baseline extramedullary disease) on-study tumor assessments may be done by laboratory studies.
s. After the end of the protocol-defined AE reporting period (see Section 6.3.1), only serious adverse events or other adverse events of concern considered related to study drug(s) or study procedures are required to be collected.

Appendix 6. Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

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 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 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 ALP.

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 ALP indicating cholestasis, viral hepatitis, or another drug).

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

IDENTIFICATION OF POTENTIAL HY'S LAW CASES

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

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

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

- Notify the sponsor representative/medical monitor by telephone and report the PHL case as an SAE of Potential Hy's law: seriousness criteria "Important medical event" and causality assessment "yes/related" or in accordance with the clinical study protocol as appropriate.
- Request a repeat of the test (new blood draw) without delay
- Complete the appropriate unscheduled laboratory 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 SAEreport following the clinical study protocol process, according to the outcome of the review.

ACTIONS REQUIRED FOR REPEAT EPISODES OF POTENTIAL HY'S LAW

This section is applicable when a subject meets PHL criteria while receiving study treatment and has already met PHL criteria at a previous on-study treatment visit. The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

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

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

- If the answer is **No**:

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

- If the answer is **Yes**:

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

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

LABORATORY TESTS

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

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

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

Reference

FDA Guidance for Industry (issued July 2009). Drug-induced liver injury: Premarketing clinical evaluation https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation.