PROTOCOL

TITLE:	An Open-label, Phase 2 Study of ACP-196 in Subjects with Mantle Cell Lymphoma
PROTOCOL NUMBER:	ACE-LY-004
STUDY DRUG:	ACP-196 (acalabrutinib)
IND NUMBER:	118717
EUDRACT NUMBER:	2014-002117-28
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AMENDMENT 7 DATE:	Version 7.0 – 18 April 2017
AMENDMENT 8 DATE:	Version 8.0 – 22 November 2017

Confidentiality Statement

PROTOCOL APPROVAL PAGE

I have carefully read Protocol ACE-LY-004 entitled “An Open-label, Phase 2 Study of ACP-196 in Subjects with Mantle Cell Lymphoma.” I agree to conduct this study as outlined herein and in compliance with Good Clinical Practices (GCP), all applicable regulatory requirements and with the ethical principles laid down in the Declaration of Helsinki. Furthermore, I understand that the sponsor, Acerta Pharma, and the 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 BV. All data pertaining to this study will be provided to Acerta Pharma BV. The policy of Acerta Pharma BV requires that any presentation or publication of study data by clinical investigators be reviewed by Acerta Pharma BV, before release, as specified in the protocol.

Principal Investigator’s Signature Date

Print Name

SUMMARY OF AMENDMENT 8

This protocol is being amended to update the risks associated with acalabrutinib treatment. This amendment provides details of additional language regarding management of suspected progressive multifocal leukoencephalopathy (PML), cytopenias, second primary malignancies, and atrial fibrillation. In addition, this amendment updates information regarding potential hemorrhage, infections, and hepatitis B reactivation. Updates have also been made to the mandatory period of contraception use following treatment with acalabrutinib; and definitions of adequate contraceptive methods.

Clarifying edits and typographical corrections have been made throughout the protocol.

The following substantive changes were made as part of this amendment:

Change	Rationale
Title Page Added: **AMENDMENT 8 DATE:** Version 8.0 – 22 November 2017	Updated protocol amendment number and date issued.
Section 1.4.1 Chemistry Added the following text (new text in **bold**) or deleted the following text (indicated by ~~strikethrough~~): Acalabrutinib is an investigational product~~, and has not been approved for marketing in any country~~. **On October 31, 2017, acalabrutinib (Calquence) was approved by United States (US) Food and Drug Administration (FDA) under Accelerated Approval for New Drug Application (NDA) 210259 for the treatment of adult patients with MCL who have received at least 1 prior therapy.**	Information was updated to reflect acalabrutinib approval for the treatment of adult patients with mantle cell lymphoma.
Section 1.5.2 Clinical Experience Deleted the following text (indicated by ~~strikethrough~~): ~~No new safety concerns were identified for acalabrutinib monotherapy based on safety data available to date~~.	To clarify, as additional safety information was added to the acalabrutinib Investigator Brochure.
Section 3.4.1 Inclusion Criteria; Synopsis Added the following text (new text in **bold**) or deleted the following text (indicated by ~~strikethrough~~): 8. Women who are sexually active and can bear children must agree to use highly effective forms of contraception during the study and for ~~90~~ **2** days after the last dose of study drug. 9. ~~Men who are sexually active and can beget children must agree to use highly effective forms of contraception, and to refrain from sperm donation, during the study and for 90 days after the last dose of study drug.~~ **This criterion has been removed as of Protocol Amendment 8.**	Text was updated for consistency across Acerta protocols and for patient safety. Male subjects taking acalabrutinib monotherapy are not required to use contraception.
Section 3.5.5 Dose Delays Added the following text (new text in **bold**) or deleted the following text (indicated by ~~strikethrough~~): ~~Any other clinically important events where dose delays may be considered appropriate by the investigator must be discussed with~~	Clarification; contact with the medical monitor is not mandatory per protocol.

Change	Rationale
~~the medical monitor.~~ **The medical monitor may be contacted to discuss dose delays related to clinically important events.**	
Section 3.7 Precautions Added new Section 3.7.1 and the following text (new text in **bold**): **Section 3.7.1 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's Brochure.** **Hemorrhage** **Bleeding events, some fatal, including central nervous system, respiratory, and gastrointestinal hemorrhage, have been reported in patients treated with acalabrutinib.** **Patients receiving antiplatelet or anticoagulant therapies may be at increased risk of hemorrhage and should be monitored for signs of bleeding. As a precaution, it is suggested per protocol that acalabrutinib be withheld for at least 3 days pre- and post-surgery.** **Patients with hemorrhage should be managed per institutional guidelines or as clinically indicated.** **Infections** **Serious infections, including fatal events, have been reported in patients treated with acalabrutinib. Patients should be monitored for signs and symptoms of infection and treated as medically appropriate.** **Hepatitis B Virus Reactivation** **Cases of hepatitis B virus (HBV) reactivation have been reported in patients treated with acalabrutinib with 1 case resulting in liver failure and death.** Subjects who are anti-HBc positive, or have a known history of hepatitis B virus (HBV) infection, should be monitored every 3 months with a quantitative PCR test for HBV DNA. Monitoring for HBV **in these subjects** should continue until 12 months after last dose of acalabrutinib. 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. Insufficient data exist regarding the safety of resuming acalabrutinib in subjects who develop HBV reactivation. **Progressive Multifocal Leukoencephalopathy** **Cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients treated with acalabrutinib. Signs and symptoms of PML may include cognitive and behavioral changes, language disturbances, visual disturbances, sensory deficits, weakness, and coordination and gait difficulties.** **If PML is suspected, hold further treatment with acalabrutinib until PML is excluded. A diagnostic evaluation may include**	Text was updated throughout the section for consistency across Acerta protocols and for patient safety.

Change	Rationale
(but is not limited to): • **Neurologic consultation** • **Brain magnetic resonance imaging (MRI)** • **Polymerase chain reaction (PCR) analysis for John Cunningham virus DNA in cerebrospinal fluid** **If PML is confirmed, permanently discontinue acalabrutinib.** **Cytopenias** **Grade 3 or 4 events of cytopenias, including neutropenia, anemia, and thrombocytopenia have occurred in patients treated with acalabrutinib. Monitor blood counts as specified in the schedule of assessments and as medically appropriate. Please refer to** Section 3.5.6 **for study drug modification guidance. Patients with cytopenias should be managed according to institutional guidelines or as clinically indicated.** **Second Primary Malignancies** **Second primary malignancies, including non-skin carcinomas, have been reported in patients treated with acalabrutinib. The most frequent second primary malignancy was skin cancer (squamous cell carcinoma of the skin). Patients with a second primary malignancy should be managed according to institutional guidelines or as clinically indicated.** **Atrial Fibrillation** **Atrial fibrillation or flutter have been reported in patients treated with acalabrutinib. Risk factors may include hypertension, diabetes mellitus, acute infections, or a previous history of atrial fibrillation. Patients with atrial fibrillation should be managed per institutional guidelines or as clinically indicated.**	
Section 3.7.1 Dietary Restrictions Renumbered to Section 3.7.2.	Renumbered.
Section 3.7.2 Surgery Deleted the following text (indicated by ~~strikethrough~~): ~~Susceptibility to bleeding has been observed with the first generation BTK inhibitor, ibrutinib (IMBRUVICA package insert). As a precaution, it is suggested that acalabrutinib be held for 3 days before and after any major surgical procedure.~~	This section was replaced by updated safety information in **Section 3.7.1 Risks Associated with Acalabrutinib Treatment** under Hemorrhage.
Section 3.7.3 Hepatitis B Virus Reactivation Deleted the following text (indicated by ~~strikethrough~~): ~~Serious or life-threatening reactivation of viral hepatitis may occur in subjects treated with a BTK inhibitor (de Jésus Ngoma 2015). Therefore, subjects with a history of HBV infection should be monitored every 3 months with a quantitative polymerase chain reaction (PCR) test for HBV DNA. HBV monitoring should last until 12 months after last dose of acalabrutinib. 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~~	Text was updated and/or moved to Section 3.7.1.

Change	Rationale
~~physician with expertise in managing hepatitis B. Insufficient data exist regarding the safety of resuming acalabrutinib in subjects who develop HBV reactivation.~~	
Section 3.7.4 Reproductive Toxicity; Synopsis Section renumbered to 3.7.3. Added the following text (new text in **bold**) or deleted the following text (indicated by ~~strikethrough~~): ~~Results of definitive reproductive toxicity studies with acalabrutinib are provided in the Acalabrutinib IB.~~ **Definition of women of non-reproductive potential:** **Women will be considered of non-reproductive potential if they are either:** **1) Postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);** **OR** **(2) Have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;** **OR** **(3) Have a congenital or acquired condition that prevents childbearing.** Women who are sexually active and can bear children must use highly effective forms of contraception during the study and for ~~90~~ **2** days after the last dose of acalabrutinib. ~~Men who are sexually active and can beget children must use highly effective forms of contraception during the study and for 90 days after the last dose of ACP-196~~. Examples of highly effective methods of contraception **are defined below.**~~include combined or progesterone-only hormonal contraceptives associated with inhibition of ovulation (implants, injectables or oral), intrauterine devices, intrauterine hormone releasing system, true sexual abstinence, bilateral tubal occlusion or vasectomized partner. Note that barrier methods with and without spermaticide, progesterone-only hormonal contraceptives where inhibition of ovulation is not the primary mode of action, periodic abstinence (eg, calendar, ovulation, symptothermal, or postovulation methods), or withdrawal are not acceptable methods of contraception.~~ […] **Definition of contraception:** **(1) Practice abstinence† from heterosexual activity;** **OR** **(2) Use (or have their partner use) highly effective contraception during heterosexual activity.** **Highly effective methods of contraception are‡:** **Single method (1 of the following is acceptable):** • **Intrauterine device** • **Vasectomy of a female subject's male partner** • **Contraceptive rod implanted into the skin**	Text was updated throughout the section for consistency across Acerta protocols and for patient safety. Based on current data as well as modeled estimates, the sponsor considers male-mediated developmental risk with acalabrutinib treatment to be very low. Modeled estimates of fetal exposures to active product ingredient levels in ejaculated material using assumptions for small molecules support that direct embryofetal exposure would be >1900-fold lower than the established no observable adverse effect level in the most sensitive species identified during embryofetal development studies.

Change	Rationale
Combination method (requires 2 of the following together): • **Male or female condom (cannot be used together)** • **Diaphragm with spermicide** • **Cervical cap with spermicide (nulliparous women only)** • **Contraceptive sponge (nulliparous women only)** • **Hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection** **†Abstinence (relative to heterosexual activity) can only be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and IECs/IRBs. Periodic abstinence (eg, calendar, ovulation, sympto-thermal, and post-ovulation methods) and withdrawal are not acceptable methods of contraception.** **‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.** Subjects should promptly notify the investigator if they, or their partner, become pregnant during this study, or within ~~90~~ **2** days after the last dose of acalabrutinib. If a female subject becomes pregnant during the treatment period, she must discontinue acalabrutinib immediately. Pregnancy in a female subject or a male subject's partner must be reported (see Section 6.2.3). ~~Male subjects must agree to refrain from sperm donation during the study and for 90 days after the last dose of study drug.~~ **Developmental and reproductive toxicology studies in rats have not identified acalabrutinib-related toxicities for fertility, reproductive success, embryofetal development or embryofetal survival. In rabbits, at dose levels which resulted in maternal toxicities skeletal variations were associated with reductions in fetal weights. Effects on parturition and post-natal development are pending. For additional details, refer to the acalabrutinib Investigator Brochure.**	
Section 3.7.5 Overdose Instructions Section renumbered to 3.7.4	Renumbered.
Section 6.2.3 Pregnancy Added the following text (new text in **bold**) or deleted the following text (indicated by ~~strikethrough~~): Any uncomplicated pregnancy that occurs in a study subject or a 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 will be reported. 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 ~~90~~ **2** days	Text was updated throughout the section for consistency across Acerta protocols and for patient safety.

Change	Rationale
after the last dose of ~~study medication~~ **acalabrutinib** will be reported, followed to conclusion, and the outcome reported, as long as the subject or partner ~~is willing~~ **has consented** to participate in follow-up.	

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ABBREVIATIONS

λ_z	terminal elimination rate constant
5PS	5-point scale
ADCC	antibody-dependent cell-mediated cytotoxicity
AE(s)	adverse event(s)
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{0-12}	area under the plasma concentration-time curve from time 0 to the 12-hour time point
AUC_{0-24}	area under the plasma concentration-time curve from time 0 to the 24-hour time point
$AUC_{0-24calc}$	area under the plasma concentration-time curve from 0 to 24 hours, calculated by doubling the value for AUC_{0-12}
AUC_{0-inf}	area under the plasma concentration-time curve from time 0 to infinity
AUC_{0-last}	area under the plasma concentration-time curve from time 0 to time t, where t is the last measurable concentration
BCR	B-cell receptor
BID	twice per day (dosing)
BTK	Bruton tyrosine kinase
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practices
CL/F	oral clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CR	complete remission (response)
CSSF	Clinical Supplies Shipping Receipt Form
CT	computed tomography
C_t	measurable concentration
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DFU	discontinuation follow-up
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity

DOR	duration of response
EC_{50}	effective concentration 50% (concentration causing half maximal effect)
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
FcR	Fc receptor
FDA	Food and Drug Administration
FDG	[^{18}F]fluorodeoxyglucose
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IHC	immunohistochemistry
IRB	Institutional Review Board
IRC	Independent Review Committee
ITK	interleukin-2-inducible T-cell kinase
LDH	lactate dehydrogenase
LDi	longest transverse diameter of a lesion
LTFU	long-term follow up
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MRD	minimal residual disease
NDA	New Drug Application
NHL	non-Hodgkin lymphoma
NK	natural killer (cells)
NR	not reached
ORR	overall response rate
OS	overall survival

PCR	polymerase chain reaction
PD	pharmacodynamics
PE	physical exam
PET	positron-emission topography
PFS	progression-free survival
PI3K	phosphoinositide-3 kinase
PK	pharmacokinetics
PML	progressive multifocal leukoencephalopathy
PPD	cross product of the LDi and perpendicular diameter
PR	partial remission (response)
PRL	partial response with lymphocytosis
PRO	patient-reported outcomes
QD	once per day (dosing)
QLQ-C30	Core Quality of Life Questionnaire (EORTC)
Q3M	every 3 months
QTc	corrected QT interval
R/R	relapsed/refractory
SAE(s)	serious adverse event(s)
SAP	Statistical Analysis Plan
SDi	shortest axis perpendicular to the LDi
SPD	sum of the product of the perpendicular diameters for multiple lesions
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal elimination half-life
T_{max}	time of the maximum plasma concentration
TTR	time to response
ULN	upper limit of normal
US	United States
Vz/F	oral volume of distribution
WHO	World Health Organization

STUDY SYNOPSIS

Protocol Number:	ACE-LY-004
Study Drug:	ACP-196 (acalabrutinib)
Protocol Title:	An Open-label, Phase 2 Study of ACP-196 in Subjects with Mantle Cell Lymphoma
Phase:	Phase 2
Comparator:	None
Background and Rationale for Study	Clinical studies have shown that targeting the B-cell receptor (BCR) signaling pathway by inhibiting Bruton tyrosine kinase (BTK) produces significant clinical benefit in patients with non-Hodgkin lymphoma (NHL), including mantle cell lymphoma (MCL). Ibrutinib, a first-generation BTK inhibitor, has been approved for the treatment of chronic lymphocytic leukemia (CLL) and MCL. The pivotal study of ibrutinib for the treatment of MCL showed that 75 of the 111 subjects (68%; 95% confidence interval [CI] 58% to 76%) had a reduction of ≥ 50% in lymphadenopathy (Wang 2013). Acerta Pharma BV (Acerta Pharma) has developed a highly selective BTK inhibitor, acalabrutinib (also known as ACP-196), that achieves significant oral bioavailability and potency in preclinical models. The purpose of this study is to evaluate the activity, safety, pharmacokinetics (PK), and pharmacodynamics (PD) of acalabrutinib administration in subjects with MCL.
Study Design:	This clinical trial is a Phase 2, multicenter, (approximately 70 global centers), open-label study in subjects with histologically documented MCL, who have relapsed after, or were refractory to, ≥ 1 (but not > 5) prior treatment regimens. Subjects will be enrolled and will take 100 mg of acalabrutinib twice per day (BID) in repeated 28-day cycles. Treatment with acalabrutinib may be continued until disease progression or an unacceptable drug-related toxicity occurs. 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 3.8 for more information on assessing disease progression under these circumstances. An early termination visit is required for any subjects who permanently discontinue study drug for any reason (except for death, lost to follow up or withdrawal of consent), including disease progression. In addition to the early termination visit, all subjects who

	discontinue study drug will have a safety follow-up visit 30 (+ 7) days after his or her last dose of acalabrutinib. All subjects will have hematology, chemistry, and urinalysis safety panels done at screening. Once dosing commences (Day 1), all subjects will be evaluated for safety, including serum chemistry and hematology, once weekly for the first 4 weeks, every 2 weeks in Cycle 2, every 4 weeks in Cycles 3 to 12, and every 12 weeks thereafter. PK/PD testing will be done in Cycles 1 and 2. Tumor assessments will be completed at 8- to 12-week intervals during the trial. Refer to Appendix 4 for a comprehensive list of study assessments and their timing. The end of trial is defined as the point when the last subject on the study exits the study for any reason.
Study Objectives:	**Primary Objective:** To determine the activity of acalabrutinib in subjects with relapsed/refractory (R/R) MCL as measured primarily by response rate. In addition, activity of acalabrutinib will be evaluated using duration of response, progression-free survival, and overall survival. **Secondary Objective:** • To characterize the safety profile of acalabrutinib • To characterize the PK profile of acalabrutinib • To evaluate the PD effects of acalabrutinib
Study Endpoints:	**Primary Endpoint:** The primary endpoint of the study is the overall response rate (ORR), defined as the proportion of subjects achieving either a partial remission (response) (PR) or complete response (CR) according to the Lugano Classification for NHL (Cheson 2014) as assessed by investigators. **Secondary Endpoints:** Efficacy: • Duration of response (DOR) • Progression-free survival (PFS) • Overall survival (OS) • Independent Review Committee (IRC)-assessed ORR, DOR and PFS per Lugano Classification Safety: • Frequency and severity of adverse events (AEs) • Frequency of AEs requiring discontinuation of study drug or dose reductions • Effect of acalabrutinib on peripheral T/B/natural killer (NK) cell counts

	• Effect of acalabrutinib on serum immunoglobulin levels
	
	Pharmacokinetics:
	• Plasma pharmacokinetics of acalabrutinib
	Exploratory Endpoints:
	• Patient reported outcomes (PRO): Health-related quality of life
	• Time to response (TTR) per Lugano Classification as assessed by investigators and IRC
	  ○ Time to initial response
	  ○ Time to best response
	  ○ Time to complete response
	• IRC-assessed ORR, DOR, TTR, and PFS per Revised Response Criteria for Malignant Lymphoma (Cheson 2007)

Sample Size:	The planned sample size for this study is 117 subjects.
Inclusion Criteria:	• Men and women ≥ 18 years of age. • Pathologically confirmed MCL, with documentation of monoclonal B cells that have a chromosome translocation t(11;14)(q13;q32) and/or overexpress cyclin D1. • Disease has relapsed after or been refractory to ≥ 1 prior therapy for MCL and now requires further treatment. • Documented failure to achieve at least PR with, or documented disease progression after, the most recent treatment regimen. • Presence of radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (defined as the presence of ≥ 1 lesion that measures ≥ 2.0 cm in the longest dimension and ≥ 1.0 cm in the longest perpendicular dimension as assessed by computed tomography [CT] scan). • At least 1, but no more than 5, prior treatment regimens for MCL. (Note: Subjects having received ≥ 2 cycles of prior treatment with bortezomib or any other commercially available proteasome inhibitor, either as single agent or as part of a combination therapy regimen, will be considered to be proteasome inhibitor exposed). • Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2. • Women who are sexually active and can bear children must agree to use highly effective forms of contraception during the study and for 2 days after the last dose of study drug. • Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty. • 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).
Exclusion Criteria:	• 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 Acerta Pharma medical monitor. • 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 ACP-196, or put the study outcomes at undue risk. • Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or corrected QT interval (QTc) > 480 msec. • Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, gastric bypass, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction. • Any immunotherapy within 4 weeks of first dose of study drug. • 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). • Prior exposure to a B-cell receptor (BCR) inhibitor (eg, BTK, phosphoinositide-3 kinase [PI3K], or SYK inhibitors) or BCL-2 inhibitor (eg, ABT-199). • Ongoing immunosuppressive therapy, including systemic or enteric corticosteroids for treatment of MCL 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. • Grade ≥ 2 toxicity (other than alopecia) continuing from prior anticancer therapy including radiation. • Known history of human immunodeficiency virus (HIV) or active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV) or any uncontrolled active systemic infection. • Major surgery within 4 weeks before first dose of ACP-196. • Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenia purpura.

	• Known history of a bleeding diathesis (eg, hemophilia, von Willebrand disease). • History of stroke or intracranial hemorrhage within 6 months before the first dose of ACP-196. • Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonist (eg, phenprocoumon) within 7 days of first dose of study drug. • Requires treatment with proton-pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). • Absolute neutrophil count (ANC) < 0.75 x 10^9/L or platelet count < 50 x 10^9/L; for subjects with disease involvement in the bone marrow, ANC < 0.50 x 10^9/L or platelet count < 30 x 10^9/L. • Creatinine > 2.5 x institutional upper limit of normal (ULN); total bilirubin > 2.5 x ULN; and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3.0 x ULN. • Breastfeeding or pregnant. • Concurrent participation in another therapeutic clinical trial. • Known central nervous system (CNS) lymphoma or leptomeningeal disease. • Requires treatment with a strong cytochrome P450 3A (CYP3A) inhibitor/inducer. • Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months prior to screening.
Dosage Form and Strength:	Acalabrutinib is provided as hard gelatin capsules prepared using standard pharmaceutical grade excipients.
Dose Regimen/Route of Administration:	Acalabrutinib is an orally administered product. Acalabrutinib can be administered with or without food. <u>Starting Dose Regimen:</u> 100 mg acalabrutinib administered 12 hours apart (BID dosing = 200 mg total daily dose)
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 gastrointestinal condition

	and a potential risk of decreased exposure to acalabrutinib. Although the effect of H2-receptor antagonists (such as famotidine or ranitidine) on acalabrutinib absorption has not been evaluated, if treatment with an H2-receptor antagonist is required, the H2-receptor antagonist should be taken approximately 2 hours after an acalabrutinib dose. The concomitant use of strong inhibitors/inducers of CYP3A with acalabrutinib should be avoided when possible. If a subject requires a strong or moderate CYP3A inhibitor while on study, monitor the subject closely for potential toxicities. Conversely, concomitant administration of acalabrutinib with a strong inducer of CYP3A has the potential to decrease exposure to acalabrutinib and could reduce efficacy. For more information on potential drug interactions with acalabrutinib, refer to the acalabrutinib Investigator Brochure (IB).
Statistical Methods:	Approximately 117 subjects meeting the stated eligibility requirements will be enrolled onto the study. A one-sample Chi-square test with a 0.025 1-sided significance level will have more than 99% power to test the null hypothesis that ORR will be ≤ 20% (not considered clinically compelling) versus the alternative hypothesis that ORR will be ≥ 40%. The sample size will provide adequate estimation utility for safety and other secondary analyses. In particular, with a sample size of 117 subjects, the probability of observing 1 or more instances of a specific AE with a true incidence rate of 1%, 2% or 5% is 69.1%, 90.6% or 99.8%, respectively. This provides reasonable assurance that events that occurring at ≥ 1% frequency can be identified in this Phase 2 study. The final analysis of primary and secondary efficacy endpoints will occur approximately 14 months after the last subject has been enrolled. A follow-up analysis will be performed when all subjects have completed their study participation.

1.0 BACKGROUND INFORMATION

1.1 ROLE OF BTK IN LYMPHOID CANCERS

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

Ibrutinib (IMBRUVICA®), a first-generation oral, small-molecule BTK inhibitor has been approved for the treatment for of several B-cell malignancies, including chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL). The pivotal study of ibrutinib for the treatment of MCL showed that 75 of the 111 treated subjects (68%) had a reduction of ≥ 50% in lymphadenopathy (Wang 2013).

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

Chemical optimization, pharmacologic characterization, and toxicologic evaluation have led to identification of acalabrutinib, an orally administered, new chemical entity that covalently inhibits BTK and shows encouraging activity and acceptable safety in nonclinical studies. Within the class of BTK inhibitors, acalabrutinib is a more selective

inhibitor of BTK than ibrutinib. Key nonclinical differentiators of acalabrutinib versus ibrutinib are:

- Acalabrutinib has been evaluated against ibrutinib in EGFR-expressing cell lines. Ibrutinib is a potent covalent inhibitor of EGFR (inhibitory concentration 50% [IC_{50}] = 5.3 nM). Ibrutinib inhibited EGFR activation in epithelial cell lines (effective concentration [EC_{50}] = 71 nM]), whereas acalabrutinib did not inhibit EGFR even at the highest concentration tested (10 µM).
- Acalabrutinib has been evaluated against ibrutinib in natural killer (NK) cell functional assays. While ibrutinib inhibited NK cell functions, including antibody-dependent cellular cytotoxicity (ADCC), lytic granule release, and cytokine production (Kohrt 2014), the in vitro functional activity of acalabrutinib-treated NK cells was preserved.
- Acalabrutinib has been evaluated against ibrutinib in an in vivo thrombus formation model. Platelets from CLL patients treated with acalabrutinib had similar thrombus formation dynamics as platelets from healthy volunteers, while platelets from ibrutinib-treated CLL patients had impaired thrombus formation.

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

1.2 MANTLE CELL LYMPHOMA

MCL is a distinct sub-type of non-Hodgkin lymphoma (NHL) comprising approximately 7% of all adult NHL, with a moderately aggressive clinical course and poor outcome. The primary cell of origin of MCL is thought to be a naive B cell of pregerminal center origin within the mantle zone of the lymph node. The incidence of MCL increases with age and an increase in incidence has been observed over time (Zhou 2008).

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

1.3 THERAPEUTIC OPTIONS FOR PREVIOUSLY-TREATED MANTLE CELL LYMPHOMA

BTK inhibition is a promising therapeutic intervention for the treatment of MCL. Ibrutinib (IMBRUVICA®), a first-in-class BTK inhibitor, has demonstrated substantial efficacy in patients with relapsed MCL based on data from a single-arm Phase 2 study of 111 patients (Wang 2013). In this study, which had an estimated median follow up of 15.3 months, the median PFS was 13.9 months (95% CI: 7.0-not reached [NR]) and ORR was 68% (CR: 21%; PR: 47%). The ORR was comparable between the bortezomib-naive and bortezomib-treated cohort of subjects, while median PFS was longer in the bortezomib-treated cohort (16.6 months) compared to the bortezomib-naive cohort (7.4 months).

The most frequently reported AEs in the study were diarrhea (50%, Grade 3: 6%), fatigue (41%, Grade 3: 5%), and nausea (31%, no Grade 3 AEs). Grade 3 and 4 hematologic AEs included neutropenia (in 16% of patients), thrombocytopenia (in 11%), and anemia (in 10%). Grade 3 bleeding AEs were reported in 5 patients, and 4 patients had subdural hematomas.

Other therapeutic agents that have received regulatory approval in relapsed MCL include bortezomib and lenalidomide. The ORR reported with both these agents is notably lower than that reported in the ibrutinib phase 2 study. In a single arm, open-label study of lenalidomide in 134 patients with MCL who had relapsed after or were refractory to bortezomib (or a bortezomib-containing regimen), the ORR was 26% (1% CR) (REVLIMID® package insert). The efficacy of bortezomib was evaluated in a single-arm open label study of 155 patients with relapsed MCL (after at least 1 prior therapy); the ORR was 31% (6% CR).

1.4 PRECLINICAL STUDIES

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

1.4.1 Chemistry

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

Acalabrutinib is an investigational product. On October 31, 2017, acalabrutinib (Calquence) was approved by United States (US) Food and Drug Administration (FDA) under Accelerated Approval for New Drug Application (NDA) 210259 for the treatment of adult patients with MCL who have received at least 1 prior therapy.

1.4.2 Mechanism of Action of Acalabrutinib

Acalabrutinib was specifically designed to be a more potent and selective inhibitor of BTK to avoid off-target side effects as seen with ibrutinib. When profiled against 395 human kinases, acalabrutinib is more selective than ibrutinib (Covey 2015). For additional details, refer to the Acalabrutinib IB.

1.4.3 Dog Lymphoma Study

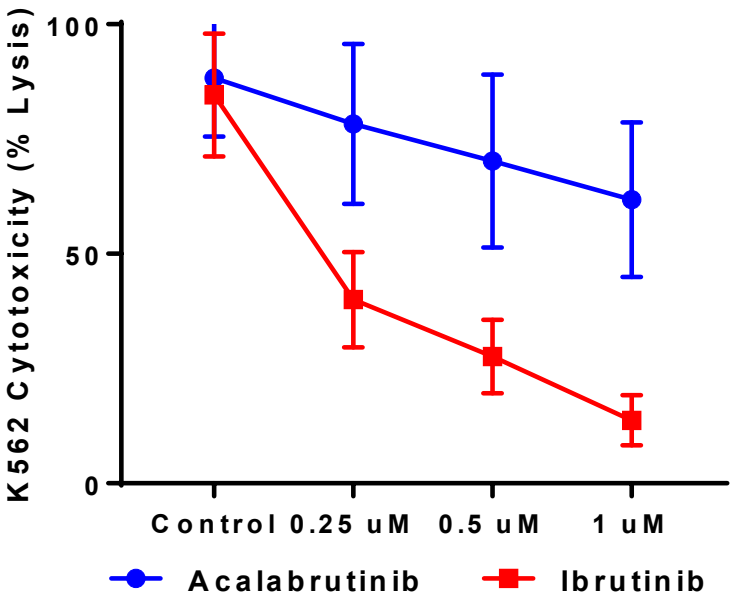
Spontaneous canine B-cell lymphoma shares many characteristics with human NHL, including diagnostic classifications and response to BTK inhibition (Honigberg 2010). The life expectancy in untreated animals with aggressive disease is ~6 weeks, thus enabling rapid assessment of drug efficacy (Vail 2004). ACP-196 was evaluated in a dose-escalation study in canine spontaneous B-cell lymphoma (Harrington 2016). Twenty dogs were enrolled in the clinical trial and treated with acalabrutinib at dosages of 2.5 to 20 mg/kg every 12 or 24 hours. Acalabrutinib was generally well tolerated, with adverse events consisting primarily of Grade 1 or 2 anorexia, weight loss, vomiting, diarrhea and lethargy. Per Veterinary Cooperative Oncology Group criteria for assessment of response in peripheral nodal lymphoma (Vail 2010), the ORR was 25% (5/20) with a median PFS of 22.5 days. Clinical benefit was observed in 30% (6/20) of dogs. These findings suggest that acalabrutinib is safe and exhibits activity in canine B-cell lymphoma patients and support the use of canine lymphoma as a relevant model for human NHL. These findings are similar to the clinical responses (ie, 1 dog with PR out of 5 dogs treated with suspected or confirmed diffuse large B-cell lymphoma [DLBCL]) observed with ibrutinib in dogs with spontaneous B-cell lymphoma (Honigberg 2010).

1.4.4 Acalabrutinib and Antibody-dependent Cell-mediated Cytotoxicity

As acalabrutinib is not an inhibitor of interleukin-2-inducible T-cell kinase (ITK) kinase, it is expected to have less activity against non-malignant cells that require ITK for development and functional activation, such as T and NK cells. ITK kinase is required for Fc receptor (FcR)-stimulated NK cell function including calcium mobilization, granule release, and overall ADCC. Anti-CD20 antibodies are standard of care drugs, often as

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

Figure 1-1. NK Cell Natural Cytotoxicity



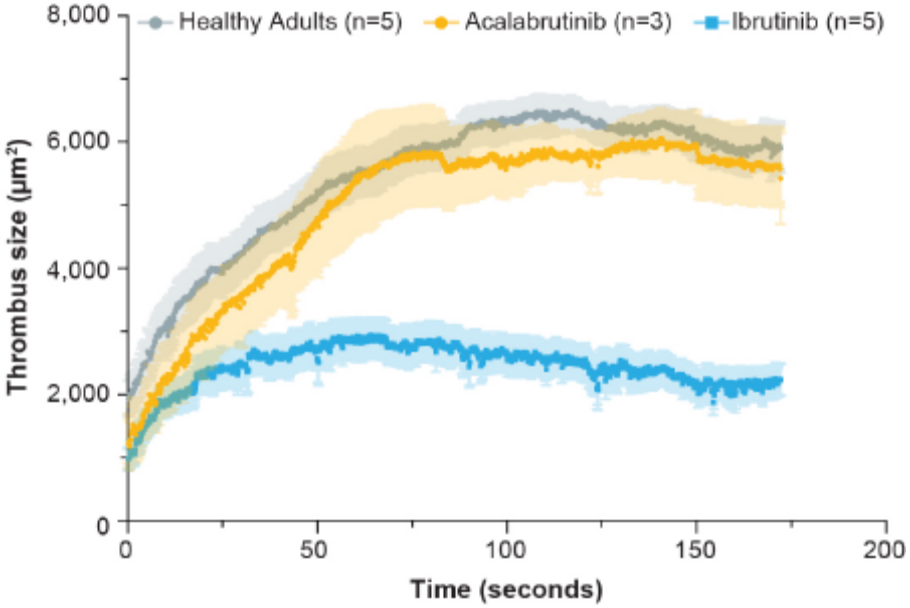
Peripheral blood mononuclear cells were cultured with ^{51}Cr labelled K562 targets at an Effector:Target ratio of 100:1 for 4 hours. Cytotoxicity was evaluated by scintillation counting of supernatants. Treatment, dose and interaction effect were significant in 2-way ANOVA (n=5 healthy donors; ibrutinib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

1.4.5 Acalabrutinib and Thrombus Formation

Ibrutinib is associated with an increased risk of bleeding (Kamel 2015; Shatzel 2017). Hence, the effects of acalabrutinib and ibrutinib were evaluated on human platelet-mediated thrombus formation by using the in vivo human thrombus formation in a von Willebrand Factor (VWFHA1) murine model, which has been previously described

(Chen 2008). The in vivo function of platelets isolated from blood of healthy volunteers (n=5), CLL patients treated with 420 mg once per day (QD) ibrutinib (n=5) or CLL patients treated with 100 mg BID acalabrutinib (n=3) was evaluated in the VWFHA1 model. Results from this study showed a reduction in platelet-vessel wall interactions of platelets from ibrutinib-treated CLL patients, but not of those from CLL patients treated with acalabrutinib (Byrd 2016).

Figure 1-2. In Vivo Thrombus Formation



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

1.4.6 Safety Pharmacology and Toxicology

In vitro and in vivo safety pharmacology and toxicology studies with acalabrutinib have demonstrated a favorable nonclinical safety profile; please refer to Acalabrutinib IB for additional details.

1.4.7 Drug-drug Interaction Potential

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

Please refer to Section 3.6 for guidance that may cause drug-drug interactions.

1.5 CLINICAL STUDIES

1.5.1 Pharmacokinetics and Pharmacodynamics of Acalabrutinib in Healthy Volunteers

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

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

1.5.2 Clinical Experience

Acerta Pharma is developing acalabrutinib for the treatment of patients with cancer or autoimmune disorders. As of 01 June 2016, acalabrutinib has been administered to more than 1600 participants in clinical studies, including subjects with hematologic malignancies, solid tumors, or rheumatoid arthritis, and participants who are healthy subjects or those with mild to moderate hepatic impairment. The safety data of acalabrutinib monotherapy are consistent among studies. Preliminary data as of 01 June 2016, based on 134 subjects with relapsed and refractory CLL, have been evaluated for tumor response based on International Working Group response criteria (Hallek 2008) as updated (Cheson 2012) to include PR with treatment-induced lymphocytosis (PRL). With a median follow up of 15.5 months, an ORR of 96.9% has been observed. Preliminary data through 01 June 2016 are also available on the first 99 sequentially enrolled subjects with previously untreated CLL. With a median follow up of 14.8 months, the ORR is 97.9% in subjects with previously untreated CLL. Overall in the ACE-CL-001 relapsed and refractory and treatment-naive cohorts, as of the 01 June 2016 data cut-off date, few subjects have experienced disease progression.

Preliminary data through 01 June 2016 are also available on the first 124 sequentially enrolled subjects with relapsed/refractory MCL who were treated with acalabrutinib on

this protocol (ACE-LY-004). With a median follow up of 6.9 months, the ORR is 80.6%, with CR in 31.5% of subjects.

For more detailed information on acalabrutinib clinical experience, please refer to the acalabrutinib IB.

1.6 BENEFITS/RISKS

Acalabrutinib is a potent, orally administered small-molecule inhibitor of BTK. A PK/PD study has been completed with acalabrutinib in healthy volunteers (ACE-HV-001; Section 1.5). The safety results showed no identified safety risks in healthy subjects receiving 1 or 2 days of acalabrutinib ≤ 100 mg. In ACE-CL-001, a study of acalabrutinib in subjects with relapsed/refractory or previously untreated CLL or Richter's syndrome, no dose-limiting toxicities (DLTs) have been reported at dosages of ≤ 400 mg QD or 100 mg and 200 mg BID. With a median follow up of 15.5 months, an ORR of 96.9% has been observed in subjects with relapsed/refractory CLL. Based on these robust results in subjects with CLL, the evaluation of acalabrutinib in subjects with relapsed/refractory MCL is warranted.

1.7 SUMMARY AND CONCLUSIONS

The design and conduct of this study is supported by an understanding of the natural history and current therapies for subjects with lymphoid cancers, knowledge of the activity and safety of the first-generation BTK inhibitor (ibrutinib) in subjects with hematologic cancers, and the available nonclinical and clinical information regarding acalabrutinib.

2.0 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

To determine the activity of acalabrutinib in subjects with R/R MCL as measured primarily by response rate. In addition, activity of acalabrutinib will be assessed by duration of response, progression-free survival, and overall survival.

2.2 SECONDARY OBJECTIVES:

- To characterize the safety profile of acalabrutinib
- To characterize the pharmacokinetic (PK) profile of acalabrutinib
- To evaluate the PD effects of acalabrutinib

3.0 STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This clinical trial is a Phase 2, multicenter, open-label study in subjects with histologically documented MCL who have relapsed after, or were refractory to, ≥ 1 (but not > 5) prior treatment regimens. Subjects will be enrolled and will take 100 mg of acalabrutinib BID in repeated 28-day cycles.

Treatment with acalabrutinib may be continued until disease progression or unacceptable drug-related toxicity, whichever occurs first. Dose modification provisions are outlined in Section 3.5.6. 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 3.8 for more information on assessing disease progression under these circumstances. An early termination visit is required for any subjects who permanently discontinue study drug for any reason (except for death, lost to follow up or withdrawal of consent), including disease progression. In addition to the early termination visit, all subjects who discontinue study drug will have a safety follow-up visit 30 (+ 7) days after his or her last dose of study drug.

All subjects will have hematology, chemistry, and urinalysis safety panels done at screening. Once dosing commences (Day 1), all subjects will be evaluated for safety, including serum chemistry and hematology once weekly for the first 4 weeks, every 2 weeks in Cycle 2, every 4 weeks in Cycles 3 to 12, and every 12 weeks thereafter. Tumor assessments will be performed at 8- to 12-week intervals throughout the study.

This study will enroll approximately 117 subjects.

Refer to Appendix 4 for a comprehensive list of study assessments and their timing. The end of trial is defined as the point when the last subject on the study exits the study for any reason.

The primary efficacy analyses will be based on investigator assessment. An Independent Review Committee (IRC) will assess the efficacy endpoints in accordance with the IRC charter provided separately from this document.

3.2 STUDY ENDPOINTS AND PARAMETERS

3.2.1 Efficacy Endpoints

Primary Endpoint:

The primary endpoint of the study is the ORR, defined as the proportion of subjects achieving either a PR or CR according to the Lugano Classification for NHL (Cheson 2014) as assessed by investigators.

Secondary Endpoints:

Efficacy:

- Duration of response (DOR)
- Progression-free survival (PFS)
- Overall survival (OS)
- IRC-assessed ORR, DOR and PFS per Lugano Classification

Safety:

- Frequency and severity of adverse events (AEs)
- Frequency of AEs requiring discontinuation of study drug or dose reductions
- Effect of acalabrutinib on peripheral T/B/NK cell counts
- Effect of acalabrutinib on serum immunoglobulin levels

Pharmacokinetics:

- Plasma pharmacokinetics of acalabrutinib

Exploratory Endpoints:

- Patient reported outcomes (PRO): Health-related quality of life
- Time to response (TTR) per Lugano Classification as assessed by investigators and IRC
    - Time to initial response
    - Time to best response
    - Time to complete response
- IRC-assessed ORR, DOR, TTR and PFS per Revised Response Criteria for Malignant Lymphoma (Cheson 2007)

3.3 RATIONALE FOR STUDY DESIGN AND DOSING REGIMEN

As described in Section 1.5, preliminary data from the ongoing Phase 1/2 study in subjects with relapsed/refractory or previously untreated CLL have shown that

acalabrutinib is well tolerated at dosages of 100 mg to 400 mg QD and 100 mg to 200 mg BID. In addition, preliminary PD data from ACE-CL-001 show that BTK occupancy with acalabrutinib, in peripheral blood, is > 95% at 4 hours after QD dosing but decreases to < 95% at 24 hours with QD dosing, while with BID dosing complete BTK occupancy (95% to 99%) is maintained over 24 hours at steady state (Byrd 2016). These data suggest that de novo synthesis of BTK can occur within 24 hours in peripheral blood cells. BID dosing may ensure BTK inhibition for the entire 24 hours, and thus may be beneficial in terms of increasing efficacy and/or decreasing development of resistance to acalabrutinib. In addition, having information regarding the safety and pharmacology of a BID schedule may support future combination studies with other drugs that are administered BID; therefore, this study has been designed to evaluate the safety, PK, PD, and activity of dosing with 100 mg BID dosing in subjects with MCL.

Approximately 117 subjects will be enrolled to this trial to receive acalabrutinib100 mg BID dose. Subjects enrolled into this trial must have received ≥ 1 appropriate treatment regimen for MCL. A maximum of 5 prior regimens is allowed.

3.4 SELECTION OF STUDY POPULATION

3.4.1 Inclusion Criteria

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

1. Men and women ≥ 18 years of age.
2. Pathologically confirmed MCL, with documentation of monoclonal B cells that have a chromosome translocation t(11;14)(q13;q32) and/or overexpress cyclin D1.
3. Disease has relapsed after or been refractory to ≥ 1 prior therapy for MCL and now requires further treatment.
4. Documented failure to achieve at least PR with, or documented disease progression after, the most recent treatment regimen.
5. Presence of radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (defined as the presence of ≥ 1 lesion that measures ≥ 2.0 cm in the longest dimension and ≥ 1.0 cm in the longest perpendicular dimension as assessed by computed tomography [CT] scan).
6. At least 1, but no more than 5, prior treatment regimens for MCL. (Note: Subjects having received ≥ 2 cycles of prior treatment with bortezomib or any other commercially available proteasome inhibitor, either as single agent or as part of a combination therapy regimen, will be considered to be proteasome inhibitor exposed).

7. Eastern Cooperative Oncology Group (ecr) performance status of ≤ 2.
8. Women who are sexually active and can bear children must agree to use highly effective forms of contraception during the study and for 2 days after the last dose of study drug.
9. This criterion has been removed as of Protocol Amendment 8.
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).

3.4.2 Exclusion Criteria

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

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 ACP-196, or put the study outcomes at undue risk.
3. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or corrected QT interval (QTc) > 480 msec.
4. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, gastric bypass, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.
5. Any immunotherapy within 4 weeks of first dose of study drug.
6. 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).
7. Prior exposure to a BCR inhibitor (eg, BTK, phosphoinositide-3 kinase [PI3K], or SYK inhibitors) or BCL-2 inhibitor (eg, ABT-199).
8. Ongoing immunosuppressive therapy, including systemic or enteric corticosteroids for treatment of MCL 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.
9. Grade ≥ 2 toxicity (other than alopecia) continuing from prior anticancer therapy including radiation.

10. Known history of human immunodeficiency virus (HIV) or active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV) or any uncontrolled active systemic infection.
11. Major surgery within 4 weeks before first dose of study drug.
12. Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenia purpura.
13. Known history of a bleeding diathesis (eg, hemophilia, von Willebrand disease).
14. History of stroke or intracranial hemorrhage within 6 months before the first dose of study drug.
15. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonist (eg, phenprocoumon) within 7 days of first dose of study drug.
16. Requires treatment with proton-pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole).
17. ANC < 0.75 $\times 10^9$/L or platelet count < 50 $\times$ 10^9/L; for subjects with disease involvement in the bone marrow, ANC < 0.50 $\times$ 10^9/L or platelet count < 30 $\times$ 10^9/L.
18. Creatinine > 2.5 × institutional upper limit of normal (ULN); total bilirubin > 2.5 × ULN; and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3.0 × ULN.
19. Breastfeeding or pregnant.
20. Concurrent participation in another therapeutic clinical trial.
21. Known central nervous system (CNS) lymphoma or leptomeningeal disease.
22. Requires treatment with a strong CYP3A inhibitor/inducer.
23. Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months prior to screening.

3.4.3 Numbers of Subjects

This study will enroll approximately 117 subjects.

3.4.4 Enrollment Procedures

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

- The study center will notify the sponsor when a clinically eligible subject is identified and is ready to screen, to ensure enrollment availability on the study.
- After the subject has signed and dated the Informed Consent Form (ICF), all screening procedures have been completed, and eligibility has been confirmed, the subject can be officially enrolled in the study.

- To enroll a subject, the study center will fax/email a completed Enrollment Confirmation Form to the sponsor. The enrollment date will be the date that the sponsor confirms enrollment.
- The sponsor will aim to fax/email a completed Enrollment Confirmation Form to the study center within 24 hours. Refer to the Pre-Screening and Enrollment Process Instructions for further details.

Treatment must begin within the screening window (Section 4.1). Study treatment is not blinded on this study.

3.5 STUDY DRUG

3.5.1 Premedications

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

3.5.2 Formulation, Packaging, and Storage

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

Acalabrutinib drug product is provided as hard gelatin capsules containing 100 mg drug substance. Acalabrutinib will be provided in white, high-density polyethylene bottles.

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

Refer to the Acalabrutinib IB for additional information regarding the drug product to be used in this trial.

3.5.3 Administration of Study Drug

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

Acalabrutinib is intended to be administered orally BID (with the second daily dose 11 hours to 13 hours after first dose) with 8 ounces (approximately 240 mL) of water

(avoid grapefruit juice and Seville orange juice due to CYP3A inhibition). Acalabrutinib may be administered with or without food. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water.

If a dose is missed, it can be taken up to 3 hours after the scheduled time with a return to the normal schedule for the next dose. If it has been > 3 hours, the dose should not be taken and the subject should take the next dose at the scheduled time. The missed dose will not be made up and must be returned to the site at the next scheduled visit.

3.5.4 Assuring Subject Compliance

Subjects undergoing PK sampling, will receive their morning Cycle 1 Day 1, Day 8, Day 15, Day 22, and Day 28 doses in the clinic. For treatments that are taken in the clinic, subjects should take the dose from the drug dispensed for them for that particular time period. All other treatments will be taken at home. Subjects will receive a diary to record the specific time each dose was taken and to record reasons for any missed doses.

Subject compliance will be assessed at every visit. The subject will be instructed to bring the diary and any remaining capsules to the clinic at their next visit. The administrator will review the diary and ask the subject if all of the capsules were administered. Any remaining or returned capsules will be counted and recorded as described in Section 7.7. Returned capsules must not be redispensed to another subject. The study staff will resupply the subject with the correct number of capsules needed for use until the next visit.

3.5.5 Dose Delays

Treatment with acalabrutinib should be held for any unmanageable, potentially study drug-related toxicity that is Grade ≥ 3 in severity. The medical monitor may be contacted to discuss dose delays related to clinically important events. Study drug may be held for a maximum of 28 consecutive days from expected dose. Study treatment should be discontinued in the event of a toxicity 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. Refer to Section 3.8 for more information on assessing disease progression under these circumstances.

3.5.6 Dose Modification and Discontinuation

The actions in Table 3-1 should be taken for the following toxicities:

- Grade 4 neutrophil count decreases (ANC < 500/μL) for > 7 days (Neutrophil growth factors are permitted per American Society of Clinical Oncology [ASCO guidelines; Smith 2015] and use must be recorded on the electronic case report form [eCRF]).
- Grade 3 platelet count decreases in the presence of significant bleeding
- Grade 4 platelet count decreases
- Grade 3 or 4 nausea, vomiting, or diarrhea, if persistent despite optimal antiemetic and/or anti-diarrheal therapy
- Any other Grade 4 toxicity or unmanageable Grade 3 toxicity.

Table 3-1. Drug Discontinuation 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

Whenever possible, any dose adjustment of acalabrutinib should be discussed between the investigator and the Acerta Pharma 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 in the appropriate eCRF.

3.6 CONCOMITANT THERAPY

3.6.1 Permitted Concomitant Therapy

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

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

3.6.2 Guideline for Use of CYP Inhibiting/Inducing Drugs

At the systemic exposure levels expected in this study, acalabrutinib inhibition of CYP metabolism is not anticipated. The concomitant use of strong inhibitors/inducers of CYP3A (Appendix 3) with acalabrutinib should be avoided when possible. If a subject requires a strong or moderate CYP3A inhibitor while on study, monitor the subject closely for potential toxicities. Conversely, concomitant administration of acalabrutinib with a strong inducer of CYP3A has the potential to decrease exposure to acalabrutinib and could reduce efficacy.

For more information on potential drug interactions with acalabrutinib, refer to the Acalabrutinib IB.

3.6.3 Guideline for Use of Drugs that Affect Gastric pH

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 gastrointestinal condition and a potential risk of decreased exposure to acalabrutinib. Although the effect of H2-receptor antagonists (such as famotidine or ranitidine) on acalabrutinib absorption has not been evaluated, if treatment with an H2-receptor antagonist is required, the H2-receptor antagonist should be taken approximately 2 hours after an acalabrutinib dose.

For more information on potential drug interactions with acalabrutinib, refer to the Acalabrutinib IB.

3.6.4 Prohibited Concomitant Therapy

Any chemotherapy, anticancer immunotherapy, corticosteroids (at dosages equivalent to prednisone > 10 mg/day), experimental therapy, or radiotherapy for treating MCL 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 (eg, phenprocoumon) are prohibited.

3.7 PRECAUTIONS

3.7.1 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's Brochure.

Hemorrhage

Bleeding events, some fatal, including central nervous system, respiratory, and gastrointestinal hemorrhage, have been reported in patients treated with acalabrutinib.

Patients receiving antiplatelet or anticoagulant therapies may be at increased risk of hemorrhage and should be monitored for signs of bleeding. As a precaution, it is suggested per protocol that acalabrutinib be withheld for at least 3 days pre- and post-surgery.

Patients with hemorrhage should be managed per institutional guidelines or as clinically indicated.

Infections

Serious infections, including fatal events, have been reported in patients treated with acalabrutinib. Patients should be monitored for signs and symptoms of infection and treated as medically appropriate.

Hepatitis B Virus Reactivation

Cases of hepatitis B virus (HBV) reactivation have been reported in patients treated with acalabrutinib with 1 case resulting in liver failure and death. Subjects who are anti-HBc positive, or have a known history of hepatitis B virus (HBV) infection, should be monitored every 3 months with a quantitative PCR test for HBV DNA. Monitoring for HBV **in these subjects** should continue until 12 months after last dose of acalabrutinib. 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. Insufficient data exist regarding the safety of resuming acalabrutinib in subjects who develop HBV reactivation.

Progressive Multifocal Leukoencephalopathy

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

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

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

If PML is confirmed, permanently discontinue acalabrutinib.

Cytopenias

Grade 3 or 4 events of cytopenias, including neutropenia, anemia, and thrombocytopenia have occurred in patients treated with acalabrutinib. Monitor blood counts as specified in the schedule of assessments and as medically appropriate. Please refer to Section 3.5.6 for study drug modification guidance. Patients with cytopenias should be managed according to institutional guidelines or as clinically indicated.

Second Primary Malignancies

Second primary malignancies, including non-skin carcinomas, have been reported in patients treated with acalabrutinib. The most frequent second primary malignancy was skin cancer (squamous cell carcinoma of the skin). Patients with a second primary malignancy should be managed according to institutional guidelines or as clinically indicated.

Atrial Fibrillation

Atrial fibrillation or flutter have been reported in patients treated with acalabrutinib. Risk factors may include hypertension, diabetes mellitus, acute infections, or a previous history of atrial fibrillation. Patients with atrial fibrillation should be managed per institutional guidelines or as clinically indicated.

3.7.2 Dietary Restrictions

Because acalabrutinib is metabolized by CYP3A (see Section 1.4.7), subjects should be strongly cautioned against excessive consumption of grapefruit, grapefruit juice, Seville oranges, or Seville orange juice (which contain potent CYP3A inhibitors) or using herbal remedies or dietary supplements (in particular, St. John's wort, which is a potent CYP3A inducer).

Acalabrutinib may be taken with or without food.

3.7.3 Reproductive Toxicity

Definition of women of non-reproductive potential:

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

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

OR

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

OR

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

Women who are sexually active and can bear children must use highly effective forms of contraception during the study and for 2 days after the last dose of acalabrutinib. Examples of highly effective methods of contraception are defined below.

Definition of contraception:

(1) Practice abstinence† from heterosexual activity;

OR

(2) Use (or have their partner use) highly effective contraception during heterosexual activity.

Highly effective methods of contraception are‡:

Single method (1 of the following is acceptable):

- Intrauterine device
- Vasectomy of a female subject's male partner
- Contraceptive rod implanted into the skin

Combination method (requires 2 of the following together):

- Male or female condom (cannot be used together)
- Diaphragm with spermicide
- Cervical cap with spermicide (nulliparous women only)
- Contraceptive sponge (nulliparous women only)
- Hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can only be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and IECs/IRBs. Periodic abstinence (eg, calendar, ovulation, sympto-thermal, and post-ovulation methods) and withdrawal are not acceptable methods of contraception.

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

Subjects should promptly notify the investigator if they, or their partner, become pregnant during this study, or within 2 days after the last dose of acalabrutinib. If a female subject becomes pregnant during the treatment period, she must discontinue acalabrutinib immediately. Pregnancy in a female subject or a male subject's partner must be reported (see Section 6.2.3).

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

3.7.4 Overdose Instructions

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

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.

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

For any subject experiencing an acalabrutinib overdose, observation for any symptomatic side effects should be instituted, and vital signs and biochemical and hematologic parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated. If the overdose ingestion is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered.

3.8 WITHDRAWAL OF SUBJECTS FROM STUDY TREATMENT

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. In addition, subjects may be withdrawn from study treatment for the following reasons:

- Study treatment should be discontinued in the event of a toxicity lasting > 28 days, unless reviewed and approved by the medical monitor.
- Any subject who starts new chemotherapy or chemoimmunotherapy for the treatment of MCL should be withdrawn from study treatment.
- Any subject who has **confirmed** objective evidence of cancer progression while receiving acalabrutinib should be withdrawn from the study treatment. If there is uncertainty regarding whether there is cancer progression, the subject may continue study treatment and remain under close observation (eg, evaluated at

4-week intervals) pending objective confirmation of progression. In particular, transient worsening of disease early in therapy or during temporary interruption of study therapy (eg, for drug-related toxicity, surgery, or intercurrent illness) may not indicate cancer progression. In such circumstances, and if medically appropriate, subjects may resume therapy and relevant clinical, laboratory, and/or radiographic assessment can be attempted to document whether tumor control can be maintained or whether cancer progression has occurred.

- 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) and survival (Section 4.4) 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 and long-term follow-up assessments 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 long-term follow-up) and the reason for discontinuation will be recorded on the appropriate CRF.

3.9 REASONS FOR STUDY EXIT

Reasons for study exit could be:

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

3.10 DATA AND SAFETY MONITORING

This trial will be monitored in accordance with the sponsor's pharmacovigilance procedures. AEs, serious adverse events (SAEs), and any subject safety questions or potential safety issues raised by the sites will be reviewed internally on an ongoing basis to identify safety concerns. The sponsor also will initiate ad hoc interactions (eg, emails, conference calls or direct contact) with investigators to obtain investigator feedback and exchange and to discuss "significant safety events" (ie, AEs leading to dose reductions, related SAEs and deaths), as well as, to discuss study progress.

4.0 STUDY ACTIVITIES AND ASSESSMENTS

The schedule of events is provided in Appendix 4. 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. Such unscheduled assessments will be captured in the protocol-specific database as appropriate. This study will primarily use central laboratory testing for laboratory evaluations. Samples from sites' local laboratories may be used if central testing is unavailable.

4.1 DESCRIPTION OF PROCEDURES

4.1.1 Informed Consent

The subject must read, understand, and sign the IRB/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.

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 responses to these treatments, will also be recorded.

4.1.3 Adverse Events

The accepted regulatory definition for an AE is provided in Section 6.1.1. All medical occurrences from the time of first dose that meet this definition must be recorded. Important additional requirements for reporting SAEs are explained in Section 6.2.

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 3.4. All screening procedures, unless otherwise indicated, should be completed within 21 days of the first dose of study drug.

4.1.6 Eastern Cooperative Oncology Group (ECOG) Performance Status

The ECOG performance index is provided in 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 exams, including tumor assessments by palpation, will be done during the treatment period and at the safety follow-up visits.

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

4.1.8 Patient Reported Outcomes (PRO)

A health-related quality of life questionnaire will be administered to each subject at screening, at the end of Cycle 2, Cycle 4, and Cycle 6; and then every 3 cycles (12 weeks) thereafter until progressive disease or use of alternative anticancer therapy.

Please refer the PRO manual for this study for instructions on administering this questionnaire.

4.1.9 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 (Cheson 2014), a bone marrow aspirate/biopsy will also be required at any time on study to confirm CR (if bone marrow was involved by lymphoma at baseline) and in some cases to confirm PR. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's Form FDA 1572. De-identified copies of all bone marrow biopsy/aspirate results may be requested by the sponsor.

For only the subjects from whom PD samples will be collected: When available, any unused bone marrow tissue will be used for PD testing. PD testing will be done by the sponsor.

4.1.10 Electrocardiogram

Subjects should be supine and resting for ≥ 10 minutes before any study-related electrocardiograms (ECGs).

4.1.11 Urine Pregnancy Test

Urine pregnancy tests will be required only for women of childbearing potential. Urine pregnancy tests will be performed at Screening; on Cycle 1 Day 1; on Day 28 of Cycles 1-12; on Day 28 of Cycles 15, 18, 21, and 24, then every 12 weeks; and at the early termination or safety follow-up visit. Testing will be done locally by use of central laboratory-provided kits.

Pregnancy testing may be done by local laboratories and can be done more frequently than the protocol-defined schedule, if required by local regulatory authorities.

4.1.12 Hematology

Hematology studies must include complete blood count (CBC) with differential and platelet counts. Testing will be done by the central laboratory.

4.1.13 Serum Chemistry

Chemistry must include albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen (BUN), bone-specific alkaline phosphatase, calcium, chloride, creatinine,

C-terminal telopeptide, glucose, lactate dehydrogenase (LDH), magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid. Testing will be done by the central laboratory.

4.1.14 Urinalysis

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

4.1.15 T/B/NK Cell Count

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

4.1.16 Serum Immunoglobulin

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

4.1.17 HBV PCR Testing

Refer to Section 3.7.1 and Appendix 4 for information on the required HBV PCR testing for subjects with a history of HBV infection. Testing will be done by local laboratories.

4.1.18 Pharmacodynamics

PD assessments will be done on up to 24 bortezomib-naive subjects and up to 24 bortezomib-exposed subjects. Blood samples and bone marrow, when available, will be used for PD testing (eg, BTK occupancy and B-cell activation). Refer to the laboratory binder for instructions on collecting and processing these samples. Testing will be done by the sponsor.

4.1.19 Pharmacokinetics

PK assessments will be done on up to 24 bortezomib-naive subjects and up to 24 bortezomib-exposed subjects. Refer to the laboratory binder for instructions on collecting and processing these samples. Testing will be performed at the central clinical laboratory. Leftover plasma samples may be used for exploratory acalabrutinib metabolite analyses. The PK sampling timepoints are provided in Table 4-1.

Table 4-1. Pharmacokinetic Sample Schedule

			HOURS POSTDOSE					
Cycle	**Day**	**Predose**	**0.5 (± 5 min)**	**0.75 (± 5 min)**	**1 (± 5 min)**	**2 (± 10 min)**	**4 (± 10 min)**	**6 (± 10 min)**
1	**1**	X	X	X	X	X	X	X
	8	X	X	X	X	X	X	X
	15, 22, 28	X			X			

All timepoints are relative to the morning dose.

4.1.20 Tumor Assessment

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

On-study tumor assessments will be done by physical exam, radiographic examination, and bone marrow assessment. Bone marrow assessments are required for confirmation of CR per clinical guidelines (see Section 4.2). Likewise, endoscopy is mandatory to confirm CR for any subjects with a documented history of gastrointestinal involvement. During treatment, CT scans with contrast (unless contraindicated) of the chest, abdomen, and pelvis and any other disease sites (eg, neck) will be performed for tumor assessments at the end of Cycle 2 (± 7 days), Cycle 4 (± 7 days), and Cycle 6; and then every 3 cycles (12 weeks) thereafter or more frequently at investigator discretion. For Cycles ≥ 6, CT and PET/CT scans may be performed within an imaging window of up to 21 days before and up to 7 days after the scheduled study visit date. During treatment, PET/CT scans will be performed at the end of Cycle 2 (± 7 days) and Cycle 6 and are required to confirm CR or as clinically indicated. Subjects with confirmed CR are not required to undergo further PET/CT scans on study unless there is suspicion of progressive disease.

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 PET/CT scan must be performed to confirm disease progression. It is recommended that disease progression identified by PET/CT alone be confirmed by an alternative imaging modality (eg, diagnostic quality CT) or by biopsy. 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.

A central imaging vendor will be used to provide independent radiologic assessments for the purposes of confirming disease progression, while investigator assessment will be used for confirming the primary endpoint. The measurements from the central imaging vendor will not be reported back to the site.

The CT portion of a PET/CT may be submitted in lieu of a dedicated CT; however, certain radiographic requirements are needed for acceptance, as described in the Site Radiology Manual, provided separately from this protocol. Magnetic resonance imaging (MRI) may be used for subjects who are either allergic to CT contrast media or have renal insufficiency that per institutional guidelines restricts the use of CT contrast media. If MRI is used, the MRI must be obtained at baseline and at all subsequent response evaluations. If MRI is required for any other reason, this must be discussed with the study medical monitor first.

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

Minimal Residual Disease (MRD) Testing

MRD testing will be performed on peripheral blood samples by a central laboratory. A blood sample is to be collected every 24 weeks (6 cycles) and again at the Early Termination visit. Baseline (pretreatment) tissue from each subject (ie, diagnostic/predose archival lymph node, bone marrow or tumor tissue) will be requested from the sites and used for baseline calibration measurements for comparison with on-treatment samples. MRD determination will be an exploratory analysis for correlation with outcome on trial and the MRD testing results will not be used for making any treatment decisions on study. Refer to the laboratory manual for processing and shipping of samples.

4.1.21 Study Drug Accountability

See Section 7.7.

4.1.22 Routine Clinical Assessments

Routine clinical assessments include physical exams, recording of symptoms, including B symptoms, and hematologic evaluations to evaluate for both AEs and assessment of disease progression. If a subject shows signs of progression, the subject may continue treatment until objective progression is confirmed. The Investigator should report any suspected disease progression to the sponsor or designee. Subjects should continue to be followed and adhere to study-related procedures until objective progression, regardless of the administration of subsequent anticancer therapy. New anticancer therapy should be withheld if clinically appropriate in the absence of objective progressive disease.

4.2 INVESTIGATOR'S ASSESSMENT OF RESPONSE TO TREATMENT

The investigator must rate the response of the subject's MCL to treatment consistent with clinical guidelines (Cheson 2014) as listed in Table 4-2.

Overall response assessments will include evaluation of physical exams, bone marrow assessments, and radiographic evaluations per the Schedule of Assessments (Appendix 4). Subjects who have signs and symptoms of progression outside of the scheduled assessment should be evaluated by the investigator with a physical exam and laboratory assessments to determine if disease progression is present. Any suspected case of disease progression should be confirmed with a CT and/or PET/CT scan, if one was not obtained, and should be reported to the sponsor or designee. It is

recommended that disease progression identified by PET/CT alone be confirmed by an alternative imaging modality (eg, diagnostic quality CT) or by biopsy. Subjects may continue study treatment until progression is confirmed by a serial exam at least 2 weeks later. In addition, when clinically appropriate, based on investigator-perceived risk/benefit assessment, a subject may continue treatment until objective progression is confirmed. New anticancer therapy should be withheld if clinically appropriate in the absence of objectively confirmed progressive disease.

Table 4-2. Response Assessment Criteria for MCL (Cheson 2014)

Response and Site	PET-CT-Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extra lymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	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 or5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm ×5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0mm
		For a node > 5 mm × 5 mm, but smaller than the normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None

Table 4-2. Response Assessment Criteria for MCL (Cheson 2014)

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

Table 4-2. Response Assessment Criteria for MCL (Cheson 2014)

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

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

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

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

4.3 EARLY TERMINATION/SAFETY FOLLOW-UP VISIT

An early termination visit is required for any subjects who permanently discontinue study drug early for any reason (except for death, lost to follow up or withdrawal of consent), including disease progression.

In addition, **all** subjects should be followed for 30 (+ 7) days after his or her last dose of study drug (ie, the "safety follow-up visit") to monitor for resolution or progression of AEs (see Section 6.2.5), and to document the occurrence of any new events, regardless of whether the subject receives a new anticancer therapy or demonstrates disease progression within this timeframe. Subjects who withdraw consent should still be encouraged to complete the safety follow-up assessments before withdrawing consent, but these assessments cannot be mandated once consent is withdrawn. The Schedule of Assessments (Appendix 4) describes the procedures required for the safety follow-up.

4.4 FOLLOW-UP FOR PROGRESSION AND SURVIVAL

Discontinuation Follow-up (DFU)

Subjects who discontinue for reasons other than progressive disease will be followed approximately every 12 weeks from the end of study treatment until disease progression or the start of alternative anticancer therapy, whichever occurs first, to assess survival and the use of alternative anticancer therapy. During this period, scans will be done approximately every 12 weeks.

Long Term Follow-up (LTFU)

Once subjects progress or start use of alternative anticancer therapy—for all subjects who have not withdrawn consent—they will be contacted approximately every 12 weeks by clinic visit or telephone, to assess survival and the use of alternative anticancer therapy until death or lost to follow up. At the time of the planned final analysis and additional milestoneanalyses, a survival sweep may be conducted. All subjects who are on study and not known to have died before the survival sweep may be contacted at that time.

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 for discrete variables) will be used to summarize data as appropriate.

Response Assessment

Response assessments will be done by the investigators and independently assessed by the IRC. The IRC will conduct response evaluations in accordance with the IRC charter (provided separately from this protocol). The response and disease progression criteria are provided in Section 4.2.

5.2 SAMPLE SIZE CONSIDERATIONS

The study will enroll approximately 117 subjects.

A one-sample Chi-square test with a 0.025 1-sided significance level will have more than 99% power to test the null hypothesis that ORR will be ≤ 20% (not considered clinically compelling) versus the alternative hypothesis that ORR will be ≥ 40%. The sample size will also provide adequate estimation utility for safety and other secondary analyses. In particular, with a sample size of 117 subjects, the probability of observing 1 or more instances of a specific AE with a true incidence rate of 1%, 2% or 5% is 69.1%, 90.6% or 99.8%, respectively. This provides reasonable assurance that events that occurring at ≥ 1% frequency can be identified in this Phase 2 study.

EAST6 (Version 6.3.1) was employed to conduct the sample size calculation.

5.3 DEFINITION OF ANALYSIS POPULATION

The safety analyses and primary efficacy analyses for all efficacy endpoints (except for DOR and TTR) will be performed on the All-treated population, defined as all enrolled subjects who receive ≥ 1 dose of study drug. The analysis of DOR and TTR will be conducted on the subset of the All-treated population who achieve CR or PR as their best overall response.

5.4 MISSING DATA HANDLING

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

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

Overall Survival: Data for subjects who have not died will be censored at the date of the last date known to be alive.

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.

5.5 ENDPOINT DATA ANALYSIS

5.5.1 Demographics and Baseline Characteristics

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

5.5.2 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.

5.5.3 Analysis of Efficacy Parameters

Primary Efficacy Endpoint

The primary efficacy endpoint is the ORR as assessed by investigators. The ORR is defined as the proportion of subjects achieving either a PR or CR, according to the Lugano Classification for NHL (Cheson 2014), as assessed by investigators. The corresponding 95% two-sided confidence interval will be derived.

Secondary Efficacy Endpoints

Duration of Response

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

Progression-free Survival

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

Overall Survival

The duration of OS will be measured from the time of first study drug administration until the date of death. Subjects who are known to be alive as of their last known status will be censored at their last date known to be alive. Kaplan-Meier methodology will be used to estimate overall survival curves and corresponding quantiles (including the median).

IRC-assessed Endpoints per Lugano Classification

ORR, DOR and PFS assessed by the IRC per Lugano Classification will be analyzed using the same analysis methods described for investigator-assessed endpoints. The discordant responses assessed by the investigator and IRC using Lugano Classification will be provided.

5.5.4 Analysis of Safety Endpoints

Safety summaries will be included in the form of tables and listings. The frequency (number and percentage) of treatment emergent AEs will be reported by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term. Summaries will also be presented by the severity of the AE (per Common Terminology Criteria for Adverse Events [CTCAE], v4.03 or higher) and by relationship to study drug.

Laboratory shift tables containing counts and percentages will be prepared by laboratory parameter. Figures of changes in laboratory parameters over time will be generated.

Results of vital sign assessments will be tabulated and summarized.

5.5.5 Analysis of Pharmacokinetic/Pharmacodynamic Endpoints

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

- $AUC_{0\text{-last}}$ Area under the plasma concentration-time curve calculated using linear trapezoidal summation from time 0 to time last, where t 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 linear trapezoidal summation.
- $AUC_{0\text{-inf}}$ Area under the plasma concentration-time curve from 0 to infinity, calculated using the formula: $AUC_{0\text{-inf}} = AUC_{0\text{-last}} + C_t / \lambda_z$, 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. If PK and PD sampling for a given subject is not performed according to protocol instructions, the 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.

5.5.6 Explorative or Correlative Analyses

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

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

5.5.7 Patient Reported Outcome (PRO)

The European Organisation for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ-C30) will be used to assess health-related quality of life. The instrument will be scored, missing values handled, and standardized scores derived (ranging from 0 to 100) as recommended in the EORTC user manual. At each assessment point, summary statistics of absolute scores and changes from baseline will be calculated for each subscale, including core and overall total score. Tables and graphs of these statistics will be generated.

5.5.8 TTR per Lugano Classification as Assessed by Investigators and IRC

TTR will be analyzed for subjects with CR/PR and is defined as the interval between the date of first dose and the date of initial documentation of a response. Time to initial response, time to best response, and time to complete response will be derived.

5.5.9 IRC-assessed Endpoints per Revised Response Criteria for Malignant Lymphoma (Cheson 2007)

ORR, DOR, TTR and PFS assessed by the IRC per Revised Response Criteria for Malignant Lymphoma (Cheson 2007) will be analyzed using the same analyses methods described for investigator-assessed endpoints.

5.6 FINAL AND FOLLOW-UP ANALYSES

The final analysis of primary and secondary efficacy endpoints will occur approximately 14 months after the last subject has been enrolled. A follow-up analysis will be performed when all subjects have completed their study participation.

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 DEFINITIONS

6.1.1 Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational (medicinal) product or other protocol-imposed intervention, 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 MCL that were not present before the AE reporting period (see Section 6.2.1).

  Complications that occur as a result of protocol-mandated interventions (eg, invasive procedures such as biopsies).

- Pre-existing medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Abnormal laboratory values should not be reported as AEs; however, any clinically significant laboratory values (defined as requiring treatment, discontinuation from the study, or dose modification) will be reported as AEs.

6.1.2 Serious Adverse Event

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

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

- It results in death (ie, the AE actually causes or leads to death).
- It is life-threatening (ie, 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 (ie, 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 (eg, may jeopardize the subject or may require medical/surgical intervention to prevent 1 of the outcomes listed above).

6.1.3 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 activity, and require systemic drug therapy or other treatment
- Grade 4 (Life-threatening or disabling AE) – experiences which cause the subject to be in imminent danger of death
- Grade 5 (Death related to AE) – experiences which result in subject death

6.2 DOCUMENTING AND REPORTING OF ADVERSE AND SERIOUS ADVERSE EVENTS

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, as outlined in the prior sections, are recorded on the eCRF. All SAEs also must be reported on the SAE form (see Section 6.2.4).

6.2.1 Adverse Event Reporting Period

The AE reporting period for this study begins when the subject receives the first dose of study drug and ends with the safety follow-up visit (or last on-treatment visit if the safety follow-up visit is not done). An exception to this reporting period is any AE occurring due to a protocol-defined screening procedure. If a fatal AE occurs beyond 30 days after the last dose of ACP-196 ***AND*** it is assessed by the investigator as related to ACP-196, it must be reported as an SAE.

SAEs considered related to study drug or study procedures occurring after the end of the AE reporting period (as defined above) must be reported.

If an SAE is present at the last study visit, the SAE should be followed to resolution or until the investigator assesses the subject as stable, or the subject is lost to follow-up or withdraws consent. Resolution/stable means the subject has returned to baseline state of health or the investigator does not expect any further improvement or worsening of the event.

6.2.2 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, detected through physical examination, clinically significant laboratory tests (ie, requiring change in study drug dose or discontinuation of study drug or any other medical intervention), or other means, will be recorded in the subject's medical record and on the AE eCRF.

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

Each recorded AE or SAE will be described by its duration (ie, start and end dates), severity, regulatory seriousness criteria, if applicable, suspected relationship to the study drug (see following guidance), and any actions taken. The causality of AEs to the study drug will be assessed by means of the question: 'Is there a reasonable possibility that the event may have been caused by the study drug?' per FDA guidance on safety reporting requirements (FDA Guidance 2012).

See Appendix 2 for more detail on assessing causality.

6.2.3 Pregnancy

The investigator should report all pregnancies in study subjects and the partners of study subjects within 24 hours of notification 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 timeline and direction for SAE reporting as described below.

Any uncomplicated pregnancy that occurs in a study subject or a 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 will be reported. 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 will be reported, followed to conclusion, and the outcome reported, as long as the subject or partner has consented to participate in follow-up.

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

Subject should be instructed to immediately notify the investigator of any pregnancies. Any women receiving acalabrutinib who become pregnant must immediately discontinue study drug. The investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Upon completion of the pregnancy, additional information on the mother, pregnancy, and baby will be collected and sent to DrugSafety@acerta-pharma.com.

6.2.4 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 electronic data capture system. If electronic SAE reporting is not available, paper SAE forms must be emailed or faxed to Acerta Pharma Drug Safety, or designee. Acerta Pharma Drug Safety may

request follow-up and other additional information from the investigator (eg, 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 electronic data capture system. If the primary cause of death is disease progression, the death due to disease progression should not be reported as an SAE. If the primary cause of death is something other than disease progression, then the death should be reported as an SAE with the primary cause of death as the event term, as death is typically the outcome of the event, not the event itself. The primary cause of death on the autopsy report should be the term reported. Autopsy and postmortem reports must be forwarded to 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 and is not listed in the current Acalabrutinib IB (ie, 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.

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

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

All AEs and SAEs that are encountered during the protocol-specified AE reporting period should be followed to resolution, or until the investigator assesses the event as stable, 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 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 International Conference on Harmonisation (ICH) Harmonised Tripartite Guidelines for Good Clinical Practices, applicable local regulations (including US Code of Federal Regulations (CFR) Title 21 and European Directive 2001/20/EC), and the ethical principles laid down in the Declaration of Helsinki.

7.2 INSTITUTIONAL REVIEW BOARD AND INDEPENDENT ETHICS COMMITTEE

The investigator will submit this protocol, the ICF, IB, and any other relevant supporting information (eg, 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 informed consent, 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) 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 § 21CFR Part 50, and other applicable national and local regulations governing informed consent. Each subject must provide a signed and dated ICF before enrollment into this study. If allowed by the protocol, a legal representative may sign the informed consent form for a subject incapable of giving consent. Signed consent forms must remain in each subject's study file and be available for verification by study monitors at any time.

In accordance with individual local and national patient privacy regulations, the investigator or designee **must** explain to each subject that in order to evaluate 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 eCRFs designed for this study according to the completion guidelines that will be provided. The investigator

will ensure that the eCRFs are accurate, complete, legible, and completed promptly. 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 a permission form authorizing the use of protected health information will also be included.

7.7 INVESTIGATIONAL STUDY DRUG ACCOUNTABILITY

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

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

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

Contents of each shipment must be visually inspected to verify the quantity and to document the condition of study drug capsules. Following the receipt of study drug, 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-004)
2. Subject identification number
3. Lot number(s) of acalabrutinib dispensed for that subject
4. Date and quantity of drug dispensed
5. Any unused drug returned by the subject

At study initiation, the monitor will evaluate and approve the site's procedure for investigational product disposal/destruction to ensure that it complies with Acerta Pharma's requirements. If the site cannot meet Acerta Pharma's requirements for disposal/destruction, arrangements will be made between the site and Acerta Pharma or its representative, for return of unused 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 1572, IRB/IEC approval letters, signed ICFs, drug accountability records, SAE forms transmitted to Acerta Pharma, subject files (source documentation) that substantiate eCRF entries, and all relevant correspondence and other documents pertaining to the conduct of the study.

An investigator shall retain records for a period of at least 2 years after the date the last marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. The investigator must notify 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. Protocol amendments 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 trial.

7.10 PUBLICATION OF STUDY RESULTS

Authorship, in general, will follow the recommendations of the International Committee of Medical Journal Editors (International Committee of Medical Journal Editors 2016).

7.11 CLINICAL TRIAL INSURANCE

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

7.12 GENERAL INVESTIGATOR RESPONSIBILITIES

The principal investigator must ensure that:

1. He or she will personally conduct or supervise the study.

2. His or her staff and all persons who assist in the conduct of the study clearly understand their responsibilities and have their names included in the Study Personnel Responsibility/Signature Log.
3. The study is conducted according to the protocol and all applicable regulations.
4. The protection of each subject's rights and welfare is maintained.
5. Signed and dated informed consent and, when applicable, permission to use protected health information are obtained from each subject before conducting nonstandard of care study procedures. If a subject or subject's legal guardian withdraws permission to use protected health information, the investigator will obtain a written request from the subject or subject's legal guardian and will ensure that no further data be collected from the subject.
6. The consent process is conducted in compliance with all applicable regulations and privacy acts.
7. The IRB/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. Electronic 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/Designee within 24 hours of knowledge and to the IRB/IEC per their requirements.

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9.0 APPENDICES

Appendix 1. Performance Status Scores

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

As published in Am J Clin Oncol:

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

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

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

Appendix 2. Adverse Event Assessment of Causality

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

No___ Yes___

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

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

The adverse event:

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

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

The adverse event:

- follows a temporal sequence from administration of study drug
- is a known response to the study drug based on clinical or 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 3. Known Strong in Vivo Inhibitors and Inducers of CYP3A

Strong Inhibitors of CYP3A[a]	Strong Inducers of CYP3A[e]
boceprevir	carbamazepine[f]
clarithromycin[b]	phenytoin[f]
conivaptin[b]	rifampin[f]
grapefruit juice[c]	St John's wort[f]
indinavir	
itraconazole[b]	
ketoconazole[b]	
lopinavir/ritonavir[b] (combination drug)	
mibefradil[d]	
nefazodone	
nelfinavir	
posaconazole	
ritonavir[b]	
saquinavir	
telaprevir	
telithromycin	
voriconazole	

a. A strong inhibitor for CYP3A is defined as an inhibitor that increases the AUC of a substrate for CYP3A by ≥ 5-fold.
b. In vivo inhibitor of P-glycoprotein.
c. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a “strong CYP3A inhibitor” when a certain preparation was used (eg, high dose, double strength) or as a “moderate CYP3A inhibitor” when another preparation was used (eg, low dose, single strength).
d. Withdrawn from the United States market because of safety reasons.
e. A strong inducer for CYP3A is defined as an inducer that results in ≥ 80% decrease in the AUC of a substrate for CYP3A.
f. In vivo inducer of P-glycoprotein.

Note: The list of drugs in these tables is not exhaustive. Any questions about drugs not on this list should be addressed to the medical monitor of the protocol.

Source:

FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Web link Accessed 21 January 2015:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#inVivo

Appendix 4. Schedule of Assessments

	Screening[a]	Cycle 1					Cycle 2		Cycle 3	Cycle 4	Cycles 5-12	Cycles 15, 18, 21, ≥ 24[b]	ET/Safety Follow Up[c]	DFU[r]	LTFU[s]
		Days (± 2)					Days (± 2)		Days (± 2)	Days (± 2)	Days (± 2)	Days (± 2)	+ 7 days	± 7 days	± 7 days
		1	8	15	22	28	15	28	28	28	28	28			
Informed consent	x														
Confirm eligibility	x														
Medical history	x														
PE[d]/Vital signs[e]/Weight	x	x	x	x	x	x	x	x	x	x	x	x	x		
B symptoms	x	x					x		x	x	x	x	x		
ECOG status	x	x	x	x	x	x	x	x	x	x	x	x	x		
ECG[f]	x														
Lab assessments:															
Urine pregnancy test[g]	x	x				x		x	x	x	x	x	x		
Hematology[h]	x	x[s]	x	x	x	x	x	x	x	x	x	x	x		
Serum chemistry[i]	x	x[s]	x	x	x	x	x	x	x	x	x	x	x		
Urinalysis[j]	x														
T/B/NK cell count[k]		x[s]						x			Cycle 6 and 12	Cycle 18 and 24, then every 24 weeks	x		
Serum Ig[l]		x[s]						x			Cycle 6 and 12	Cycle 18 and 24, then every 24 weeks	x		
Bone marrow (aspirate/biopsy)[p]	x										To confirm CR	To confirm CR			
HBV PCR[v]									x		Q3M	x		Q3M	Q3M
Response assessments[q]															
CT	x							x		x	Cycle 6, 9, and 12	x		x	
PET/CT	x							x			Cycle 6 & to confirm CR	To confirm CR			
MRD[w]	x											X (every 24 weeks/6 cycles)	x		

Pharmacodynamics		x[m]	x[m]			x[n]		x[n]					X[aa]		
Pharmacokinetics[o]		x	x	x	x	x									
Acalabrutinib dispensed		x				x		x	x	x	x	x			
Study drug compliance		x	x	x	x	x	x	x	x	x	x	x			
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x		
Adverse events[x]		x	x	x	x	x	x	x	x	x	x	x	x	x	x
EORTC (QLQ-C30) Questionnaire[u]	x							x		x	Cycle 6, 9, and 12	x			
Survival Status[z]															x

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CR = complete remission; CT = computed tomography; DFU = discontinuation follow-up; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ET = early termination; HBV = hepatitis B virus; Ig = immunoglobulin; LDH = lactate dehydrogenase; LTFU = long-term follow-up; mos = months; MRD = minimal residual disease; PCR = polymerase chain reaction; PD = pharmacodynamic; PE = physical exam; PET = positron-emission tomography; PK = pharmacokinetic; PRO = patient reported outcomes; Q3M = every 3 months.

Footnotes for ACE-LY-004 Schedule of Study Activities*:*

a. Screening tests should be performed within 21 days before the first administration of study drug, unless otherwise indicated.
b. Treatment with acalabrutinib may be continued until disease progression or unacceptable drug-related toxicity, whichever occurs first. After Cycle 24, subjects will continue to have scheduled visits every 12 weeks as outlined on the schedule of assessments.
c. An early termination visit will be done for subjects who permanently discontinue study drug early for any reason (except for death, lost to follow up or withdrawal of consent). In addition, a 30-day (+ 7 days) safety follow-up visit is required for **all** subjects after his or her last dose of study drug to monitor for AEs, regardless of whether the subject receives a new anticancer therapy or demonstrates disease progression within this timeframe.
d. The screening physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. Symptom-directed physical exams, including tumor assessments by palpation, are done thereafter.
e. Vital signs (blood pressure, heart rate, and temperature) will be assessed after the subject has rested in the sitting position.
f. Subjects should be in supine position and resting for ≥ 10 minutes before study-related ECGs.
g. Women of childbearing potential only. Urine pregnancy tests will be performed at Screening, on Cycle 1 Day 1; on Day 28 of Cycles 1-12; on Day 28 of Cycles 15, 18, 21, and 24, then every 12 weeks; and at the early termination or safety follow-up visit. Testing will be done locally by use of central laboratory-provided kits. Pregnancy testing may be done by local laboratories and can be done more frequently than the protocol-defined schedule, if required by local regulatory authorities.
h. Hematology includes complete blood count with differential and platelet counts. Cycle 1 Day 1 hematology does not need to be repeated if screening hematology was within 5 days.
i. Serum chemistry: albumin, alkaline phosphatase, alanine transaminase (ALT), aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen (BUN), bone-specific alkaline phosphatase, calcium, chloride, creatinine, c-terminal telopeptide, glucose, lactate dehydrogenase (LDH), magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid. Cycle 1 Day 1 serum chemistry does not need to be repeated if screening chemistry was within 5 days.
j. Urinalysis: pH, ketones, specific gravity, bilirubin, protein, blood, and glucose.
k. T/B/NK cell count (ie, CD3, CD4, CD8, CD19, CD16/56). During Cycles ≥ 5, only done at the end of Cycles 6, 12, 18, and 24, then every 24 weeks thereafter.
l. Serum immunoglobulin: IgG, IgM, IgA. During Cycles ≥ 5, only done at the end of Cycles 6, 12, 18, and 24, then every 24 weeks thereafter.

m. Pharmacodynamic (PD) assessments will be done on up to 24 bortezomib-naive subjects and up to 24 bortezomib-exposed subjects. PD samples are drawn predose and 4 hours (± 10 minutes) postdose on the days indicated (relative to the morning dose).
n. Pharmacodynamic (PD) assessments will be done on up to 24 bortezomib-naive subjects and up to 24 bortezomib-exposed subjects. PD samples are drawn predose on the days indicated
o. Pharmacokinetic (PK) assessments will be done on up to 24 bortezomib-naive subjects and up to 24 bortezomib-exposed subjects. PK samples are drawn per Table 4-1, and timepoints are relative to the morning dose.
p. Bone marrow are required for confirmation of CR (if bone marrow was involved by lymphoma at baseline) per clinical guidelines (see Section 4.2).
q. A pretreatment computed tomography (CT) scan with contrast (unless contraindicated) is required of the chest, abdomen, and pelvis and any other disease sites (eg, neck) within 30 days before the first dose of study drug. A pretreatment positron-emission tomography (PET)/CT scan within 60 days from first dose of study drug is also required. During treatment, CT scans with contrast (unless contraindicated) will be performed for tumor assessments at the end of Cycle 2 (± 7 days), Cycle 4 (± 7 days), and Cycle 6; and then every 3 cycles (12 weeks) thereafter, or more frequently at the investigator's discretion. For Cycles ≥ 6, CT and PET/CT scans may be performed within an imaging window of up to 21 days before and up to 7 days after the scheduled study visit date. During treatment, PET/CT scans will be performed at the end of Cycle 2 (± 7 days) and Cycle 6 as well as any time to confirm CR or as clinically indicated. Subjects with confirmed CR are not required to undergo further PET/CT scans on study unless there is suspicion of progressive disease. Endoscopy is mandatory to confirm CR for any subjects with a documented history of gastrointestinal involvement.
r. Subjects who discontinue will be followed approximately every 12 weeks from the date of last dose until study exit to assess survival and the use of alternative anticancer therapy. During this period, CT scans will be done approximately every 12 weeks until disease progression or until the start of alternative anticancer therapy.
s. Subjects who progress or start alternative anticancer therapy will be followed approximately every 12 weeks until study exit to assess survival and the use of alternative anticancer therapy
t. The indicated samples at this timepoint (Cycle 1 Day 1) must be drawn predose.
u. Patient reported outcome assessment will be done at screening, at the end of Cycle 2, Cycle 4, and Cycle 6; and then every 3 cycles (12 weeks) thereafter until progressive disease or use of alternative anticancer therapy.
v. Subjects who are hepatitis B core antibody positive (or have a known history of HBV infection) should be monitored Q3M with a quantitative PCR test for HBV DNA. HBV monitoring should last until 12 months after last dose of study drug. Any subject with a rising viral load (above lower limit of detection) should discontinue study drug and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B.
w. MRD testing will be performed on peripheral blood samples and pretreatment archival tissue by a central laboratory. A blood sample is to be collected every 24 weeks (6 cycles) for all subjects and for those subjects who permanently discontinued early, a blood sample is to be collected at the ET visit. An archival tissue sample is to be collected (ie, tumor tissue in form of lymph node, peripheral blood or bone marrow sample) before study drug administration to identify the malignant clone and calibrate measurements for comparison with on-treatment samples.
x. After the end of the protocol-defined adverse event reporting period (see Section 6.2.1), only serious adverse events considered related to study drug(s) or study procedures are required to be collected.
z. Survival status should be assessed at the time of the planned final analysis and additional milestone analyses as applicable.
aa. Pharmacodynamics to be assessed at the ET visit for patients who permanently discontinued early.