PROTOCOL

TITLE	An Open-label, Phase 2 Study of ACP-196 in Subjects with Waldenström Macroglobulinemia[1]
PROTOCOL NUMBER	ACE-WM-001
STUDY DRUG	ACP-196 (acalabrutinib)
IND NUMBER	118717
EUDRACT NUMBER	2014-003212-36
SPONSOR MEDICAL MONITOR	PPD PPD Phone: PPD Email: PPD
SPONSOR	Acerta Pharma BV PPD 5349 AB Oss The Netherlands
PROTOCOL DATE	Version 0.0 – 12 May 2014
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Confidentiality Statement

[1] In Italy only, the original protocol title "An Open-label, Phase 1b/2 Study of ACP-196 in Subjects with Waldenström Macroglobulinemia" remains in effect.

PROTOCOL APPROVAL

VERSION 9.0

I have carefully read Protocol ACE-WM-001 entitled "An Open-label, Phase 2 Study of ACP-196 in Subjects with Waldenström Macroglobulinemia[2]." I agree to conduct this study as outlined herein and in compliance with Good Clinical Practices, all applicable regulatory requirements, and with the ethical principles laid down in the Declaration of Helsinki. Furthermore, I understand that the Sponsor, Acerta Pharma, and the Institutional Review Board/ Independent Ethics Committee must approve any changes to the protocol in writing before implementation.

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

Principal Investigator's Signature Date

Print Name

[2] In Italy only, the original protocol title "An Open-label, Phase 1b/2 Study of ACP-196 in Subjects with Waldenström Macroglobulinemia" remains in effect.

SUMMARY OF AMENDMENT 9.0

This protocol was amended to add the possibility of a rollover or safety extension study and to clarify the time points for the follow-up analyses. Updates to the clinical experience and safety information were made to align with the current acalabrutinib Investigator Brochure and to maintain consistency across Acerta's acalabrutinib protocols.

Appendix 6 (Management of Study Procedures During COVID-19 Pandemic) was added to consolidate guidance for subject safety and ongoing access to medical care and investigational product during the global COVID-19 pandemic.

Clarifying edits and typographical changes have been made throughout the protocol. The substantive changes that were made as part of this amendment are noted in the table below.

Sections Impacted	Rationale
PROTOCOL TITLE PAGE	Updated medical monitor and contact information.
STUDY SYNOPSIS	Updated the Synopsis to reflect changes in the protocol.
Section 1.1 Role of BTK in Lymphoid Cancers	Updated information on Calquence approval in CLL and SLL.
Section 1.3.2 Clinical Experience	Updated based on the current acalabrutinib Investigator Brochure.
Section 3.1 Description of Study	Added text for the rollover or safety extension study to ensure treatment continuation, with visit assessments per the rollover or extension protocol and alignment with other acalabrutinib protocols.
Section 3.5.3 Administration of Study Drug Section 3.7.6 Dietary Restrictions	Modified language regarding grapefruit and Seville oranges, and herbal remedies or dietary supplements that contain CYP3A inhibitors or inducers to align with the Core Data Sheet.
Section 3.7 Risks Associated with Acalabrutinib Treatment	Updated section to align with the current acalabrutinib Investigator Brochure.
Section 3.7.7 Reproductive Toxicity	Updated highly effective methods of contraception language to align with the current acalabrutinib Investigator Brochure.
Section 5.7 Primary and Final Analysis	Revised text to clarify time points for follow-up analyses.
Section 6.2.1 Adverse Event Reporting Period	Revised text to provide consistency across Acerta's acalabrutinib protocols.

Sections Impacted	Rationale
Section 6.2.3 Second Primary Malignancies	Added new section to provide guidance for reporting second primary malignancies for consistency across Acerta's acalabrutinib protocols.
Section 6.2.4 Pregnancy Section 6.2.5 Expedited Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest Section 7.12 General Investigator Responsibilities	Instructions for reporting of SAEs and pregnancy were updated to clarify that reporting should be made to the AstraZeneca Representative instead of Acerta Pharma Drug Safety.
Section 6.2.5 Type and Duration of Follow-up of Subjects After Adverse Events	Deleted section because this is covered by the new language in Section 6.2.1.
Appendix 6 Management of Study Procedures During Pandemic Section 4.0 STUDY ACTIVITIES AND ASSESSMENTS	Added appendix to consolidate guidance for subject safety and ongoing access to medical care and investigational product during the global COVID-19 pandemic.

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ABBREVIATIONS

Abbreviation	Definition
λ_z	terminal elimination rate constant
ACP-196	acalabrutinib
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{0\text{-}12}$	area under the plasma concentration-time curve from 0 to 12 hours, calculated using linear trapezoidal summation
$AUC_{0\text{-}24calc}$	area under the plasma concentration-time curve from 0 to 24 hours, calculated by doubling the value for $AUC_{0\text{-}12}$
$AUC_{0\text{-}inf}$	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
$AUC_{0\text{-}last}$	area under the plasma concentration-time curve calculated using linear trapezoidal summation from time 0 to time last, where “last” is the time of the last measurable concentration
BCL-2	B-cell lymphoma 2
BCR	B-cell receptor
BID	twice a day
BTK	Bruton tyrosine kinase
CL/F	oral clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed plasma concentration
CR	complete response
CRF	case report form
CSSF	Clinical Supplies Shipping Receipt Form
Ct	concentration
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DOR	duration of overall response
ECG	electrocardiogram

Abbreviation	Definition
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
FDA	Food and Drug Administration
HBV	hepatitis B virus
HCV	hepatitis C virus
hERG	human ether-à-go-go-related gene
ICF	informed consent form
IEC	Independent Ethics Committee
IFE	immunofixation electrophoresis
Ig	immunoglobulin
IND	Investigational New Drug
IRB	Institutional Review Board
ITK	interleukin-2-inducible T-cell kinase
IWWM	International Workshops on Waldenström Macroglobulinemia
MedDRA	Medical Dictionary for Regulatory Activities
MR	minor response
MRI	magnetic resonance imaging
NK	natural killer (cells)
NOAEL	no observable adverse effect level
OATP	organic-anion-transporting polypeptide
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	pharmacodynamic
PFS	progression-free survival
PI3K	phosphoinositide-3 kinase
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PR	partial response
PRO	Patient-Reported Outcomes
QD	once a day
QTc	corrected QT interval
SAE	serious adverse event

Abbreviation	Definition
SFU	safety follow-up
SPEP	serum protein electrophoresis
SUSAR	Suspected Unexpected Serious Adverse Reaction (report)
SYK	spleen tyrosine kinase
$t_{½}$	terminal elimination half-life
T_{max}	time to maximum drug concentration
TT	treatment termination
ULN	upper limit of normal
VGPR	very good partial response
VWF	von Willebrand Factor
Vz/F	volume of distribution
WM	Waldenström macroglobulinemia

STUDY SYNOPSIS

Protocol Number:	ACE-WM-001
Study Drug:	ACP-196 (acalabrutinib)
Protocol Title:	An Open-label, Phase 2 Study of ACP-196 in Subjects with Waldenström Macroglobulinemia[3]
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, including Waldenström macroglobulinemia (WM). Ibrutinib (IMBRUVICA®), an oral, small-molecule BTK inhibitor has been approved for the treatment for chronic lymphocytic leukemia (CLL), mantle cell lymphoma, and WM. Acerta Pharma BV (Acerta Pharma) has developed a novel BTK inhibitor, acalabrutinib, that achieves significant oral bioavailability and potency in preclinical models. The purpose of this study is to evaluate the safety, pharmacokinetics, cci [redacted] and activity of acalabrutinib in treating subjects with WM.
Study Design:	This study is a multicenter (approximately 30 global centers) open-label clinical study evaluating the safety and efficacy of acalabrutinib cci [redacted] in subjects with previously treated WM (N=76) using a Simon's optimal 2-stage design. In addition, a small cohort (N=8–12) of subjects with treatment-naive WM will be enrolled as an exploratory cohort to determine the preliminary safety and efficacy of acalabrutinib in this patient population. In The Netherlands and France, enrollment for the untreated WM cohort will begin after efficacy has been confirmed in Stage 1 of the Simon's optimal 2-stage design; in other locations, both previously treated and untreated cohorts will be enrolled simultaneously. Twenty-eight days of study drug administration is 1 cycle. Treatment with acalabrutinib may be continued until disease progression or an unacceptable drug-related toxicity occurs. Dose modification provisions are provided in the 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. A

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	treatment termination (TT) visit is required for safety assessments for any subjects who permanently discontinue study drug for any reason (except for death, loss to follow-up or withdrawal of consent), including disease progression, and should be scheduled within 7 days of his or her last dose of study drug, if possible. In addition to the TT visit, all subjects who discontinue acalabrutinib will have a safety follow-up (SFU) visit 30 (+7) days after the last dose of study drug to monitor for resolution or progression of adverse events (AEs) and to document the occurrence of any new events, regardless of whether the subject receives a new anticancer therapy or demonstrates disease progression within this timeframe. Refer to Section 4.4 for information on follow-up for progression and survival. All subjects will have standard 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 according to Appendix 4. Pharmacokinetic (PK) testing will be done in Cycle 1 only, and CCI testing will be done in Cycle 1 and Cycle 2. PKCCI will be done on all subjects in the treatment-naive cohort and on up to 12 subjects in the previously treated cohort. Assessments for efficacy will be completed throughout the study as per Appendix 4. A single, interim analysis (see Section 5.6) of overall response rate (ORR) will be performed when subjects from Stage 1 (28 subjects) are evaluable for response. Refer to Appendix 4 for a comprehensive list of study assessments and their timing. The end of study is defined as the last subject's last visit. The sponsor may terminate the study at any time. The study duration is expected to be approximately 6 years from enrollment of the last subject. Subjects who are still on treatment at the time of final analysis and who are deriving clinical benefit from acalabrutinib treatment may continue treatment. At the time of the final data cutoff and database closure, subjects who remain in this study may be transitioned to a separate rollover study or remain within this study protocol for continued access to study drug. For those subjects who are eligible to continue to receive acalabrutinib after database closure, there will be no further data collection other than reporting of SAEs. Access to study treatment within this study protocol will enable continued treatment with visit assessments per standard of care, whereas the separate rollover study will enable treatment continuation with visit assessments and data collection per the rollover study protocol. A study schema is provided at the end of this synopsis.

Study Objectives:	**Primary Objective:** To determine the ORR of acalabrutinib in subjects with WM as assessed by the investigator. **Secondary Objectives:** • To determine the duration of overall response (DOR) of acalabrutinib assessed by the investigator • To determine the progression-free survival (PFS) of acalabrutinib assessed by the investigator • To determine the overall survival (OS) of acalabrutinib • To characterize the PK profile of acalabrutinib • To characterize the safety of acalabrutinib • To evaluate the effect of acalabrutinib in health-related quality of life CCI [redacted]
Study Endpoints:	**Co-Primary endpoints:** • ORR, defined as a subject achieving a minor response (MR) or better according to the response assessment criteria for WM (Owen 2013), as assessed by the investigator • ORR, defined as a subject achieving a MR or better according to the response assessment criteria defined by modified 3rd International Workshops on Waldenström Macroglobulinemia (IWWM) workshop criteria (Kimby 2006), as assessed by the investigator **Secondary endpoints:** Efficacy: • DOR assessed by the investigator using response assessment criteria for WM (Owen 2013) and modified 3rd IWWM workshop criteria (Kimby 2006) • PFS assessed by the investigator using response assessment criteria for WM (Owen 2013) and modified 3rd IWWM workshop criteria (Kimby 2006) • OS • Effect of acalabrutinib on peripheral T/B/natural killer (NK) cell counts • Effect of acalabrutinib on serum immunoglobulin levels Safety: • Frequency, severity, and relatedness of AEs

	• Frequency of AEs requiring discontinuation of study drug or dose reductions Pharmacokinetics: • Plasma pharmacokinetics of acalabrutinib Patient-Reported Outcomes (PRO): • Health-related quality of life CCI [redacted]
Pharmacokinetic Parameters:	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 "last" is the time of the last measurable concentration (Ct). • $AUC_{0\text{-}12}$: 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
CCI [redacted]	

Sample Size:	The Simon's optimal 2-stage portion of the study for evaluation of efficacy in subjects with previously treated WM will be approximately 76 subjects. The exploratory cohort in subjects with treatment-naive WM will enroll approximately 8 to 12 subjects.

Inclusion Criteria:	• Men and women ≥18 years of age.
	• Previously treated cohort only: A confirmed diagnosis of WM, which has relapsed after, or been refractory to ≥1 prior therapy for WM and which requires treatment.
	• Treatment-naive cohort only: A confirmed diagnosis of treatment-naive WM in subjects who require treatment and do not want to receive chemoimmunotherapy or have comorbidities that would preclude chemoimmunotherapy such as:
	  ○ Symptomatic hyperviscosity with an immunoglobulin (Ig) M ≥5,000 mg/dL
	  ○ Disease-related neuropathy
	• Serum concentration of IgM, as measured by serum protein electrophoresis (SPEP) and immunofixation electrophoresis (IFE), that exceeds the upper limits of normal **or** measurable nodal WM (defined as the presence of ≥1 lymph node that measures ≥2.0 cm in the longest diameter and ≥1.0 cm in the longest perpendicular diameter).
	• 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 acalabrutinib. Highly effective forms of contraception are defined in Section 3.7.7.
	• 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).

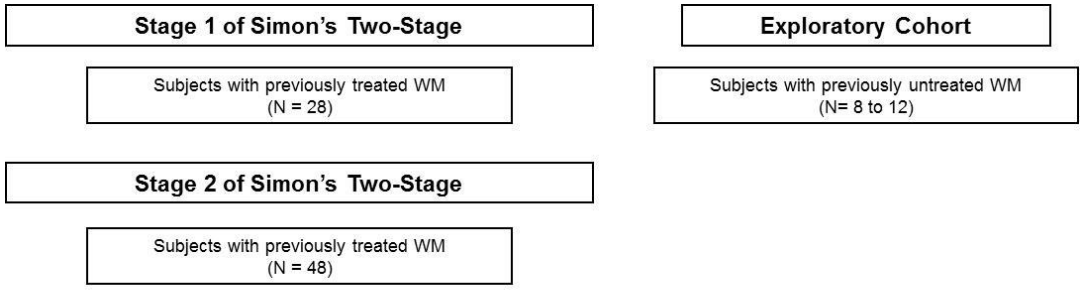
Exclusion Criteria:	• Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject has been disease free for ≥2 years or which will not limit survival to <2 years.

	Note: These cases must be discussed with the 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 acalabrutinib, 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 or gastric bypass, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction. • Any immunotherapy within 4 weeks of first dose of study drug. • For subjects with recent chemotherapy or experimental therapy, the first dose of study drug must occur after 5 times the half-life of the agent(s). • Prior exposure to a BCR inhibitor (e.g., BTK, phosphoinositide-3 kinase [PI3K], or spleen tyrosine kinase [SYK] inhibitors) or B-cell lymphoma 2 (BCL-2) inhibitor (e.g., ABT-199). • Ongoing immunosuppressive therapy, including systemic or enteric corticosteroids, for treatment of WM 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 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 study drug. • Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenia purpura. • History of a bleeding diathesis (e.g., hemophilia, von Willebrand disease).

	• History of stroke or intracranial hemorrhage within 6 months before the first dose of acalabrutinib. • Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonist (e.g., phenprocoumon) within 28 days of first dose of study drug. • Requires treatment with proton-pump inhibitors (e.g., 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 ULN; total bilirubin >2.5 x ULN; or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3.0 x ULN. • Lactating or pregnant. • Concurrent participation in another therapeutic clinical study.
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. Acalabrutinib CCI [redacted] It is recommended that acalabrutinib be taken as close to the scheduled time as possible (preferably within 1 hour). However, if a dose is missed, it can be taken up to 3 hours after the scheduled time with a return to the normal schedule with the following 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. Concomitant use of strong inhibitors/inducers of cytochrome P450 (CYP) 3A 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.
Statistical Methods:	Simon's optimal 2-stage design for assessment of efficacy in previously treated subjects: This study will test the null hypothesis that the ORR is ≤35% against the alternative hypothesis that it is ≥55%. Using Simon's optimal 2-stage design, a total sample size of 76 subjects has power 90% to achieve a 1-sided significance level of 0.025. In Stage 1, 28 subjects will be evaluated for efficacy. If ≥12 out of 28 subjects (43%) achieve an ORR (includes a MR or better), then the study will continue to full enrollment. In Stage 2, a further 48 subjects will be enrolled. With Simon's optimal 2-stage design, an ORR of ≥46% (i.e., ≥35 subjects responding out of 76 subjects evaluated) will achieve a 1-sided significance level of ≤0.025. Exploratory cohort for assessment of efficacy in treatment-naive subjects: No formal statistical tests of hypotheses will be performed. Eight to 12 evaluable subjects will be enrolled in this cohort for evaluation of preliminary efficacy and safety in this patient population. Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions for discrete variables) will be used to summarize data, as appropriate.

STUDY SCHEMA



Note: All sites can start exploratory cohort concurrent with Stage 1, except for sites in the Netherlands, which must wait until after Stage 1.

WM=Waldenström macroglobulinemia.

1.0 BACKGROUND INFORMATION

1.1 Role of BTK in Lymphoid Cancers

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®), an oral, small-molecule BTK inhibitor has been approved for the treatment for CLL, mantle cell lymphoma (MCL), and WM.

While highly potent in inhibiting BTK, ibrutinib has also shown in vitro activity against other kinases with a cysteine in the same position as Cys481 in BTK to which the drug covalently binds. The inhibition of epidermal growth factor receptor (EGFR) is also observed in cellular assays and may be the cause of ibrutinib-related AEs of diarrhea and rash (IMBRUVICA package insert). In addition, ibrutinib is a substrate for CYP3A4; inhibition of CYP3A causes a 29-fold increase in C_{max} and 24-fold increase in 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 (also known as ACP-196), an orally bioavailable, 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 (EC_{50}=5.3 nM). Acalabrutinib did not inhibit EGFR, even at the highest concentration tested (10 µM).

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

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.

Acalabrutinib (CALQUENCE®) is an investigational product. CALQUENCE has been approved in the United States and other markets for the treatment of adult patients with MCL who have received at least one prior therapy, CLL, and small lymphocytic lymphoma (SLL).

1.2 Preclinical Studies

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

1.2.1 Chemistry

CCI [redacted]

For clinical testing, acalabrutinib has been manufactured and formulated according to current Good Manufacturing Practices.

1.2.2 Mechanism of Action of Acalabrutinib

CCI [redacted]

CCI [redacted] For additional details, refer to the acalabrutinib Investigator Brochure.

1.2.3 Dog Lymphoma Study

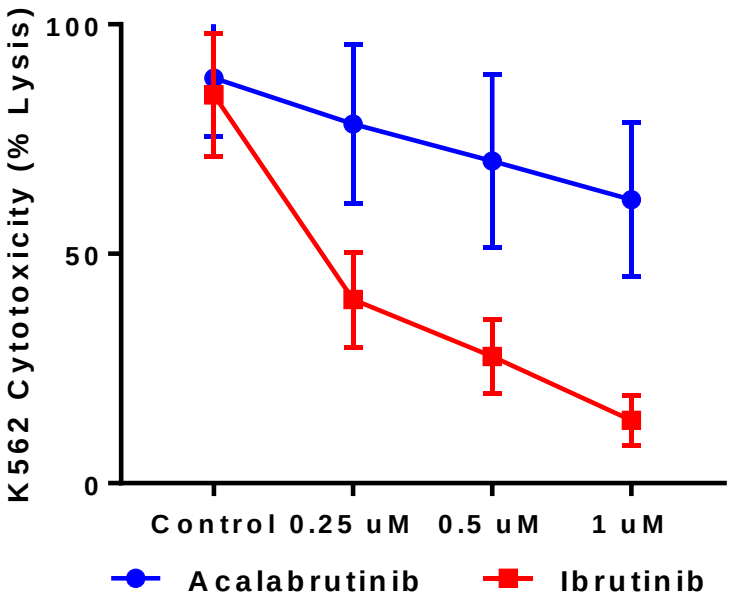
Spontaneous canine B-cell lymphoma shares many characteristics with human non-Hodgkin lymphoma, including diagnostic classifications and response to BTK inhibition (Honigberg 2010). The life expectancy in untreated animals with aggressive disease is ~6 weeks, thus enabling rapid assessment of drug efficacy (Vail 2004). Acalabrutinib was evaluated in a dose-escalation study in canine spontaneous B-cell lymphoma (Harrington 2016). Twenty dogs were enrolled in the study and treated with acalabrutinib at dosages of 2.5 to 20 mg/kg every 12 or 24 hours. Acalabrutinib was generally well tolerated, with AEs consisting primarily of grade 1 or 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 non-Hodgkin lymphoma. These findings are similar to the responses (i.e., 1 dog with partial response (PR) out of 5 dogs treated with suspected or confirmed diffuse large B-cell lymphoma) observed with ibrutinib in dogs with spontaneous B-cell lymphoma (Honigberg 2010).

1.2.4 Acalabrutinib and Antibody-dependent Cell-mediated Cytotoxicity

As acalabrutinib is not an inhibitor of 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-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. NK Cell Natural Cytotoxicity

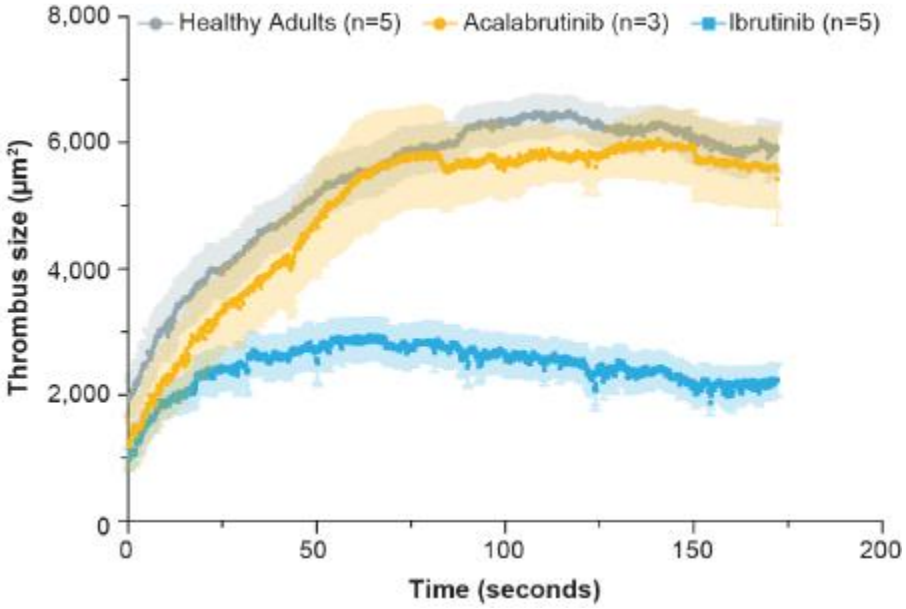


Peripheral blood mononuclear cells were cultured with ^{51}Cr labelled K562 targets at an E:T ratio of 100:1 for 4 hours. Cytotoxicity was evaluated by scintillation counting of supernatants. Treatment, dose and interaction effect were significant in 2-way ANOVA (n=5 healthy donors; ibrutinib v. acalabrutinib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

1.2.5 Acalabrutinib and Thrombus Formation

Ibrutinib is associated with an increased risk of bleeding (Kamel 2014). Hence, the effects of acalabrutinib and ibrutinib were evaluated on human platelet-mediated thrombus formation by using the in vivo human thrombus formation in a von Willebrand Factor (VWF^{HA1}) murine model, which has been previously described (Chen 2008). The in vivo function of platelets isolated from blood of healthy volunteers (n=5), CLL subjects treated with CCI [redacted] ibrutinib (n=5) or CLL subjects treated with CCI [redacted] acalabrutinib (n=3) was evaluated in the VWF^{HA1} model. Results from this study showed a reduction in platelet-vessel wall interactions of platelets from ibrutinib-treated CLL subjects, but not of those from CLL subjects treated with acalabrutinib (Byrd 2016).

Figure 2. In Vivo Thrombus Formation



Platelets from patients treated with ibrutinib CCI (n=5) or acalabrutinib CCI (n=3) were evaluated for their ability to support thrombus formation in laser injured arterioles of VWF^{HA1} mice. Freshly isolated platelets from healthy volunteers (n=5) were used as non-drug treated controls. A minimum of 4 arterioles per mouse was used to assess thrombus formation for each patient/volunteer sample. Median fluorescence intensity as a function of time is provided in the figure (shading denotes standard error of the median).

1.2.6 Safety Pharmacology

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

When screened at 10 µM in binding assays evaluating interactions with 80 known pharmacologic targets such as G-protein-coupled receptors, nuclear receptors, proteases, and ion channels, acalabrutinib shows significant activity only against the A3 adenosine receptor; follow-up dose-response experiments indicated an IC_{50} of 4.5 µM, suggesting a low clinical risk of off-target effects.

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

Acalabrutinib was well tolerated in standard in vivo Good Laboratory Practices studies of pharmacologic safety. A functional observation battery in rats at doses through 300 mg/kg (the highest dose level) revealed no adverse effects on neurobehavioral effects or body temperature at any dose level. A study of respiratory function in rats also

indicated no treatment-related adverse effects at doses through 300 mg/kg (the highest dose level). In a cardiovascular function study in awake telemeterized male beagle dogs, single doses of acalabrutinib at dose levels through 30 mg/kg (the highest dose level) induced no meaningful changes in body temperature, cardiovascular, or ECG (including QT interval) parameters. The results suggest that acalabrutinib is unlikely to cause serious off-target effects or adverse effects on critical organ systems.

1.2.7 Drug-Drug Interaction Potential

Based on available preclinical and clinical data, acalabrutinib is cleared by multiple CYP and non-CYP metabolic pathways. CYP3A-mediated oxidation appears to be a major route of metabolism in humans. In excretion studies in preclinical species, metabolites were mainly related to direct conjugation of acalabrutinib with glutathione and conjugation with glutathione in vitro was mediated primarily by human glutathione transferases GSTM1 and GSTM2. Metabolites also arose from oxidation (CYP3A) and amide hydrolysis, or combinations thereof.

In a healthy volunteer study (ACE-HV-001), the effect of co-administration of a potent CYP3A and P-glycoprotein inhibitor, itraconazole, on the plasma levels of acalabrutinib was evaluated. The mean plasma acalabrutinib C_{max} and $AUC_{0\text{-}inf}$ values increased 3.7-fold and 5.1-fold, respectively, in the presence of itraconazole relative to no pretreatment. In a healthy volunteer study (ACE-HV-004) rifampin, a strong CYP3A inducer, dosed at CCI for 9 days decreased AUC to 23% of values obtained with acalabrutinib dosed alone. Refer to Section 3.6.2 for detailed recommendations on concomitant administration of acalabrutinib with strong CYP3A inhibitors or inducers.

Results from a healthy volunteer study (ACE-HV-004) also showed drugs that reduce gastric acidity can lower acalabrutinib exposure. Refer to Section 3.6.3 for detailed recommendations regarding co-administration of acalabrutinib with agents that reduce gastric acidity.

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

Results from drug transporter studies suggest that acalabrutinib is not anticipated to alter the PK of other therapeutic agents that are substrates for multidrug resistance protein 1, organic-anion-transporting polypeptide (OATP)1B1, OATP1B3, OAT1, OAT3, and OCT2. Acalabrutinib is a substrate and inhibitor of breast cancer resistance protein and may alter the PK of coadministered breast cancer resistance protein substrates.

Refer to the acalabrutinib Investigator Brochure for additional details on acalabrutinib PK; absorption, distribution, metabolism, and excretion; and drug interaction studies.

1.2.8 In Vivo General Toxicology

The systemic toxicity of acalabrutinib has been fully evaluated in repeat-dose sub-chronic studies in mice, rats and dogs, reproductive toxicity studies in rats and rabbits, and ongoing chronic studies in rats and dogs. The pivotal GLP studies were 28- and 91-day repeat dose studies in rats and dogs, each with recovery periods to assess the reversibility of observed changes.

In rats, 100 mg/kg/day was selected initially to represent the highest non-severely toxic dose; however, in subsequent studies the 100 mg/kg/day dose level was determined to be a no observable adverse effect level (NOAEL). In rats, the target organs of toxicity were the kidney, liver and heart.

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

In rats and dogs, no adverse ECG or histopathologic cardiovascular effects were noted at the planned conclusion of the sub-chronic studies or in the rat chronic toxicity study. However, in 5 of 6 rats from the 4-week study that died early, slight to moderate necrosis of the myocardium and/or white blood cell infiltration/inflammation of the myocardium were noted on microscopic examination of the hearts.

1.3 Clinical Studies

A list of completed and ongoing clinical studies is provided in the acalabrutinib Investigator Brochure.

1.3.1 Pharmacokinetics and Pharmacodynamics of Acalabrutinib in Clinical Pharmacology Studies

PK properties of acalabrutinib in healthy adult volunteers were evaluated after oral administration of CCI [redacted] (ACE-HV-001). Acalabrutinib T_{max} values were between 0.5 and 1.0 hour for all dose cohorts, and were independent of dose level. Mean $t_{1/2}$ values ranged from 0.97 hour to 2.1 hours. Exposure increases were approximately linear from CCI [redacted] up to and beyond

therapeutic doses of CCI Rapid elimination was observed. Acalabrutinib does not accumulate with daily administration. Similar PK results were observed in subjects with CLL treated with acalabrutinib. In healthy subjects and subjects with CLL, dose-related increases in BTK occupancy were attained, and relatively high BTK occupancy (>90%) was observed with a CCI

Administration of acalabrutinib with a high-fat, high-calorie meal did not have a clinically significant effect on exposure so acalabrutinib can be taken without regard to meals. In healthy volunteer studies, agents that lowered gastric acidity (e.g., calcium carbonate and omeprazole) lowered exposure of concomitantly administered acalabrutinib. Acalabrutinib is unlikely to be a perpetrator of a drug-drug interaction at the level of inhibition or induction of CYP isoforms. However, the mean plasma acalabrutinib C_{max} and AUC values increased 3.7- and 5.1-fold, respectively, in the presence of itraconazole, a strong CYP3A inhibitor, relative to no pretreatment. Rifampin, a strong CYP3A inducer, dosed at CCI for 9 days decreased AUC to 23% of values obtained with acalabrutinib dosed alone.

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

1.3.2 Clinical Experience

Acalabrutinib has been studied in a broad range of clinical studies, including subjects with hematologic malignancies, solid tumors, or rheumatoid arthritis, and participants who are healthy volunteers or with mild to moderate hepatic impairment. No serious adverse events (SAEs) have been reported in the completed hepatic impairment study (Study ACE-HI-001) or in the healthy volunteer studies. Current details on the clinical experience for acalabrutinib, including updated data from clinical safety and efficacy studies with acalabrutinib, are presented in the Investigator Brochure.

Study ACE-CL-001 (NCT02029443) is an ongoing, nonrandomized, sequential group, dose-escalation Phase 1/2 study in subjects with CLL, including subjects with relapsed/refractory CLL, treatment-naive subjects, ibrutinib-intolerant subjects, and subjects with Richter's syndrome or prolymphocytic leukemia transformation. As of 01 December 2017, 134 subjects with relapsed/refractory CLL had 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. After a median on-study time of 31.8 months, an ORR of 96.2% was observed in subjects with

relapsed/refractory CLL. Preliminary data as of 04 September 2018 for 99 enrolled subjects with treatment-naive CLL showed an ORR of 99% after a median on-study time of 41.6 months.

Preliminary efficacy data through 13 February 2018 are available for 106 subjects with previously treated WM who received acalabrutinib monotherapy in the present study. The median time on study was 35.8 months. The ORR was 93.4% under both the modified 3rd International Workshops on Waldenström Macroglobulinemia (IWWM-3) and the 6th IWWM response criteria (Kimby 2006 and Owen 2013, respectively).

1.4 Benefit/Risk

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 1.3.2). The safety results showed no identified safety risks in healthy subjects receiving 1 or 2 days of acalabrutinib CCI In Study ACE-CL-001, no dose-limiting toxicities were reported at dosages of CCI Based on the results for subjects with CLL and other B-cell malignancies, the evaluation of acalabrutinib in subjects with WM is warranted.

1.5 Summary and Conclusions

The design and conduct of this study are supported by an understanding of the natural history and current therapies for subjects with lymphoid cancers; knowledge of the efficacy 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 ORR of acalabrutinib in subjects with WM as assessed by the investigator.

2.2 Secondary Objectives

- To determine the DOR of acalabrutinib assessed by the investigator
- To determine the PFS of acalabrutinib assessed by the investigator
- To determine the OS of acalabrutinib
- To characterize the PK profile of acalabrutinib

- To characterize the safety of acalabrutinib
- To evaluate the effect of acalabrutinib in health-related quality of life

2.3 CCI [redacted]

CCI [redacted]

3.0 STUDY DESIGN

3.1 Description of Study

This study is a multicenter (approximately 30 global centers), open-label clinical study evaluating the safety and efficacy of acalabrutinib CCI [redacted] in subjects with previously treated WM (N=76) using a Simon's optimal 2-stage design (Simon 1989). In addition, a small cohort (N=8–12) of subjects with treatment-naive WM will be enrolled as an exploratory cohort to determine the preliminary safety and efficacy of acalabrutinib in this patient population. In The Netherlands and France, enrollment for the untreated WM cohort will begin after efficacy has been confirmed in Stage 1 of the Simon's optimal 2-stage design; in other locations, both previously treated and untreated cohorts will be enrolled simultaneously.

Twenty-eight days of study drug administration is 1 cycle. Treatment with acalabrutinib may be continued until disease progression or an unacceptable drug-related toxicity occurs. Dose modification provisions are provided in the protocol (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. A TT visit is required for safety assessments for any subjects who permanently discontinue study drug for any reason (except for death, loss to follow-up, or withdrawal of consent), including disease progression, and should be scheduled within 7 days of his or her last dose of study drug, if possible. In addition to the TT visit, all subjects who discontinue acalabrutinib will have a SFU visit 30 (+7) days after the last dose of study drug to monitor for resolution or progression of AEs and to document the occurrence of any new events, regardless of whether the subject receives a new anticancer therapy or demonstrates disease progression within this timeframe. Refer to Section 4.4 for information on follow-up for progression and survival.

All subjects will have standard 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 according to Appendix 4. PK testing will be

done in Cycle 1 only and [redacted] testing will be done in Cycle 1 and Cycle 2. PK [redacted] will be done on all subjects in the treatment-naive cohort and on up to 12 subjects in the previously treated cohort.

Assessments for efficacy will be completed throughout the study as per Appendix 4.

A single interim analysis (see Section 5.6) of ORR will be performed when subjects from Stage 1 (28 subjects) are evaluable for response.

Refer to Appendix 4 for a comprehensive list of study assessments and their timing. The end of study is defined as the time of the last subject's last visit. The sponsor may terminate the study at any time. The study duration is expected to be approximately 6 years from enrollment of the last subject.

Subjects who are still on treatment at the time of final analysis and who are deriving clinical benefit from acalabrutinib treatment may continue treatment. At the time of the final data cutoff and database closure, subjects who remain in this study may be transitioned to a separate rollover study or remain within this study protocol for continued access to study drug. Once all active subjects are eligible to continue to receive acalabrutinib after database closure, there will be no further data collection other than reporting of SAEs per Section 6.2. Access to study treatment within this study protocol will enable continued treatment with visit assessments per standard of care, whereas the separate rollover study will enable treatment continuation with visit assessments and data collection per the rollover study protocol.

3.2 Study Endpoints and Parameters

3.2.1 Co-Primary Endpoints

- ORR, defined as a subject achieving a MR or better according to the response assessment criteria for WM (Owen 2013), as assessed by the investigator
- ORR, defined as a subject achieving a MR or better according to the response assessment criteria defined by modified 3rd IWWM workshop criteria (Kimby 2006), as assessed by the investigator

3.2.2 Secondary Endpoints

Efficacy:

- DOR assessed by the investigator using response assessment criteria for WM (Owen 2013) and modified 3rd IWWM workshop criteria (Kimby 2006)

- PFS assessed by the investigator using response assessment criteria for WM (Owen 2013) and modified 3rd IWWM workshop criteria (Kimby 2006)
- OS
- Effect of acalabrutinib on peripheral T/B/NK cell counts
- Effect of acalabrutinib on serum immunoglobulin levels

Safety:

- Frequency, severity, and relatedness of AEs
- Frequency of AEs requiring discontinuation of study drug or dose reductions

Pharmacokinetics:

- Plasma pharmacokinetics of acalabrutinib

PRO:

- Health-related quality of life

3.2.3 CCI

CCI

3.2.4 Safety Parameters

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

For consistency of interpretation, AEs will be coded using the MedDRA, and the severity of AEs and laboratory abnormalities will be graded using the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 or higher. Standard definitions for seriousness will be applied (see Section 6.1).

3.2.5 Pharmacokinetic CCI Parameters

Standard PK parameters for acalabrutinib in plasma will be evaluated in this study. A full description of the PK parameters is provided in Section 5.5.4.

CCI

3.3 Rationale for Study Design and Dosing Regimen

A total daily dose of CCI of acalabrutinib CCI has been selected for this study. Preliminary PK data from ACE-CL-001 as described in Section 1.3.2 suggest a plateauing of exposure after CCI PD results from this study also show similar BTK occupancy for CCI Therefore, based on PK/PD, safety, and efficacy results of the Phase 1/2 study, a CCI will be evaluated. For the most recent information on acalabrutinib study results and dosing rationale, refer to the acalabrutinib Investigator Brochure.

3.4 Selection of Study Population

3.4.1 Inclusion Criteria

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

1. Men and women ≥ 18 years of age.
2. Previously treated cohort only: A confirmed diagnosis of WM, which has relapsed after, or been refractory to ≥1 prior therapy for WM and which requires treatment
3. Previously untreated cohort only: A confirmed diagnosis of previously untreated WM in subjects who require treatment and do not want to receive chemoimmunotherapy or have comorbidities that would preclude chemoimmunotherapy such as:
    - Symptomatic hyperviscosity with an IgM ≥5,000 mg/dL
    - Disease-related neuropathy
4. Serum concentration of IgM, as measured by SPEP and IFE, that exceeds the upper limits of normal or measurable nodal WM (defined as the presence of ≥1 lymph node that measures ≥2.0 cm in the longest diameter and ≥1.0 cm in the longest perpendicular diameter).
5. ECOG performance status of ≤2.
6. 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 acalabrutinib. Highly effective forms of contraception are defined in Section 3.7.7.
7. This criterion was removed as of Protocol Amendment 7.
8. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty.
9. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national 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 acalabrutinib, or put the study outcomes at undue risk.
3. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or QTc >480 msec.
4. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel or 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. For subjects with recent chemotherapy or experimental therapy, the first dose of study drug must occur after 5 times the half-life of the agent(s).
7. Prior exposure to a BCR inhibitor (e.g., BTK, PI3K, or SYK inhibitors) or BCL-2 inhibitors (e.g., ABT-199).
8. Ongoing immunosuppressive therapy, including systemic or enteric corticosteroids for treatment of WM 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 HIV or active infection with 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. History of a bleeding diathesis (e.g., hemophilia, von Willebrand disease).
14. History of stroke or intracranial hemorrhage within 6 months before the first dose of acalabrutinib.
15. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon) within 28 days of first dose of study drug.
16. Requires treatment with proton-pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole)

17. 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 x10^9/L.
18. Creatinine >2.5 x institutional ULN; total bilirubin >2.5 x ULN; or AST or ALT >3.0 x ULN.
19. Lactating or pregnant.
20. Concurrent participation in another therapeutic clinical trial.

3.4.3 Replacement of Subjects

Any subject who does not complete Cycle 2 (at least 8 weeks) may be replaced at the discretion of the study investigator and sponsor.

3.4.4 Enrollment Procedures

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

- Notify the sponsor when a clinically eligible subject is identified and 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.

Treatment must begin within the 21-day screening window (Section 4.1) and after the site has received approval from the sponsor. 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 Good Manufacturing Practices 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 capsules contain CCI [redacted] Acalabrutinib will be provided in white, high-density polyethylene bottles.

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

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 CCI [redacted]

Acalabrutinib is intended to be administered orally CCI [redacted] 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.

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

3.5.4 Assuring Subject Compliance

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. Any other clinically important events where dose delays may be considered appropriate by the investigator must be discussed with the medical monitor. Study drug may be held for a maximum of 28 consecutive days from expected dose due to toxicity. Study treatment should be discontinued in the event of a toxicity lasting >28 days, unless reviewed and approved by the medical monitor.

Note: Temporary withholding of study drug for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. 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 1should be taken for the following toxicities:

- Grade 4 ANC (<500/µL) for >7 days (Neutrophil growth factors are permitted per American Society of Clinical Oncology guidelines [Smith 2015] and use must be recorded on the case report form [CRF]).
- Grade 3 platelet decreases in presence of significant bleeding
- Grade 4 platelet 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 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
3rd	Hold acalabrutinib until recovery to Grade ≤1 or baseline; restart at CCI [redacted]
4th	Discontinue acalabrutinib

As appropriate, certain laboratory abnormalities may warrant more frequent monitoring (e.g., once per week) until abnormalities have recovered to Grade ≤1. If acalabrutinib is reduced for apparent treatment-related toxicity, the dose need not be re-escalated, even if there is minimal or no toxicity with the reduced dose. However, if the subject tolerates a reduced dose of acalabrutinib for ≥4 weeks then the dose may be increased to the next higher dose level, at the discretion of the investigator. Such re-escalation may be particularly warranted if further evaluation reveals that the AE that led to the dose reduction was not treatment related. However, the maximum dose of acalabrutinib is CCI [redacted] for this protocol.

For full study treatment discontinuation criteria, refer to Section 3.8.

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, alkalinization of urine, 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. However, as discussed in Section 1.2.7 concomitant administration of acalabrutinib with a strong or moderate CYP3A inhibitor increased exposure by approximately 5-fold. Consequently, the concomitant use of strong inhibitors/inducers of CYP3A (Appendix 3) 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 a

strong inducer of CYP3A has the potential to decrease exposure of acalabrutinib and could reduce efficacy.

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.

3.6.4 Prohibited Concomitant Therapy

Any chemotherapy, immunotherapy, kinase inhibitors, bone marrow transplantation, experimental therapy, and radiotherapy are prohibited. High-dose corticosteroids used to treat underlying WM are not allowed on study.

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

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

3.7 Risks Associated with Acalabrutinib Treatment

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

3.7.1 Hemorrhage

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

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

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

3.7.2 Infections

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

Consider prophylaxis in subjects who are at increased risk for opportunistic infections. Subjects should be monitored for signs and symptoms of infection and treated as medically appropriate. Subjects with infection events should be managed according to institutional guidelines with maximal supportive care and diagnostic evaluations as clinically indicated.

3.7.2.1 Progressive Multifocal Leukoencephalopathy

Cases of 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 treatment until PML is excluded. A diagnostic evaluation may include (but is not limited to):

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

If PML is confirmed, permanently discontinue acalabrutinib.

3.7.2.2 Hepatitis B Virus Reactivation

Serious or life-threatening reactivation of viral hepatitis may occur in subjects treated with a BTK inhibitor (de Jésus Ngoma 2015). Cases of HBV reactivation have been reported in patients treated with acalabrutinib with 1 case resulting in liver failure and death. Therefore, subjects with a history of HBV infection should be monitored monthly with a quantitative PCR test for HBV DNA from Cycle 6 to Cycle 48 or early discontinuation, and then every 3 months thereafter. Monitoring 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.

3.7.3 Cytopenia

Grade 3 or 4 events of cytopenia including neutropenia, anemia, and thrombocytopenia have occurred in clinical studies with acalabrutinib. Monitor blood counts as specified in the schedule of assessments and as medically appropriate. Refer to Section 3.5.6 for study drug modification guidance.

Subjects with cytopenias should be managed according to institutional guidelines with maximal supportive care and diagnostic evaluations as clinically indicated. Subjects should be closely monitored as appropriate.

3.7.4 Second Primary Malignancies

Events of second primary malignancies, including non-skin carcinomas, have occurred in clinical studies with acalabrutinib. The most frequently reported second primary malignancy was skin cancer.

Subjects should be monitored for signs and symptoms of malignancy. Subjects who develop a second primary malignancy should be managed according to institutional guidelines with diagnostic evaluations as clinically indicated and it may be necessary for subjects to permanently discontinue study treatment. Continuation of acalabrutinib treatment should be discussed with the medical monitor.

Please refer to Section 6.2.3 for reporting guidance for second primary malignancies.

3.7.5 Atrial Fibrillation

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

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

3.7.6 Dietary Restrictions

Because acalabrutinib is metabolized by CYP3A (see Section 1.2.7), subjects should be strongly cautioned against using herbal remedies or dietary supplements that contain potent CYP3A inhibitors or CYP3A inducers (in particular, St. John's wort, which is a potent CYP3A4 inducer). Acalabrutinib can be taken with or without food. Based on results from Study ACE-HV-112, consumption of grapefruit juice, which can result in CYP3A inhibition, will not result in substantially increased exposure to acalabrutinib. Therefore, restrictions on grapefruit juice or Seville orange consumption are not necessary. For more detailed information on drug-drug interaction potential for acalabrutinib, refer to the acalabrutinib Investigator Brochure.

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

3.7.7 Reproductive Toxicity

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. For additional details, refer to the acalabrutinib Investigator Brochure.

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 level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of

12 months of amenorrhea, a single follicle stimulating hormone measurement is insufficient.);

OR

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

OR

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

Definition of highly effective methods of contraception:

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

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

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

Abstinence (relative to heterosexual activity) can only be used as the sole method of contraception if it is consistently employed during the entire period of risk associated with the study treatments as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and Independent Ethics Committees (IECs)/ Institutional Review Board (IRBs). Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, and postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together as an effective method of contraception.

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

Female subjects with reproductive potential (see definition above) who are sexually active must use highly effective methods of contraception during the study and for 2 days after the last dose of acalabrutinib. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

Subjects should promptly notify the investigator if they, or their partners, become pregnant during this study. Female subjects must also notify the investigator if they become pregnant within 2 days after the last dose of acalabrutinib. If a woman becomes pregnant during the treatment period, she must discontinue acalabrutinib immediately. Pregnancy in a female subject or a male subject's partner must be reported as outlined in Section 6.2.4.

3.7.8 Overdose Instructions

For any subject experiencing an acalabrutinib overdose (ingestion of more than the recommended dosage), observation for any symptomatic side effects should be instituted, and vital signs 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.

The medical monitor should be contacted if an acalabrutinib overdose occurs.

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 requiring a dose hold lasting >28 days, unless reviewed and approved by the medical monitor.

- 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 true cancer progression, the subject may continue study treatment and remain under close observation (e.g., evaluated at 4-week intervals) pending confirmation of progression. In particular, transient worsening of disease early in therapy or during temporary interruption of study therapy (e.g., 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 radiologic 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.

3.9 Reasons for Study Exit

Reasons for study exit include:

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

3.10 Data and Safety Monitoring

This study will be monitored in accordance with the sponsor's pharmacovigilance procedures. AEs and SAEs will be reviewed internally on an ongoing basis to identify safety concerns. Conference calls with the investigators will be conducted as needed to discuss study progress, obtain investigator feedback and exchange, and discuss

"significant safety events" (i.e., AEs that led to dose modifications, treatment-related SAEs, and deaths).

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. See Appendix 6 for management of study procedures during the COVID-19 pandemic.

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, also will be recorded.

4.1.3 Adverse Events

The accepted regulatory definition for an AE is provided in Section 6.1. The AE reporting period is described in Section 6.2.1. Important additional requirements for reporting SAEs are explained in Section 6.1.5.

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 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. The nervous system examination will include attention to neurologic signs and symptoms of PML.

Symptom-directed physical examinations, including extramedullary disease assessments by palpation, will be done during the treatment period and at the SFU visits.

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

4.1.8 Patient-Reported Outcomes

A health-related quality of life questionnaire will be administered to each subject as outlined in the schedule of assessments. 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. This study requires a bone marrow aspirate and biopsy at the end of Cycle 2 and Cycle 12, which must be done within 4 weeks of the contemporaneous radiologic evaluation. Per the current response criteria (Owen 2013), a bone marrow aspirate and biopsy will also be required at any time on study to confirm a complete response (CR). Pathologic review of the bone marrow aspirate and biopsy

will be performed by a central laboratory (or local laboratory, if central laboratory is unavailable) for confirmation of WM diagnosis.

CCI [redacted]

4.1.10 Electrocardiogram

Subjects should be in supine position and resting for ≥10 minutes before study-related ECGs.

4.1.11 Urine or Serum Pregnancy Test

Pregnancy tests will be required only for women of childbearing potential. 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 with differential and platelet and reticulocyte counts. Testing will be done by the central laboratory.

4.1.13 Serum Chemistry

Serum chemistry must include albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen, bone-specific alkaline phosphatase, calcium, chloride, creatinine, c-terminal telopeptide, glucose, lactate dehydrogenase, magnesium, phosphate, potassium, sodium, total bilirubin, total protein, and uric acid. If an unscheduled ECG is done at any time, then an electrolyte panel (i.e., calcium, magnesium, and potassium) must be done to coincide with the ECG testing. Testing will be done by the central laboratory.

See Appendix 5 for actions required in cases of increases in liver biochemistry and evaluation of Hy's law.

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 and Serum M protein

Testing for IgG, IgM, IgA, and serum M protein levels (by SPEP and IFE) will be done by the central laboratory.

4.1.17 HBV PCR Testing

Refer to Section 3.7.2.2 and Appendix 4 for information on the required HBV PCR testing for subjects with a history of HBV infection.

4.1.18 CCI

CCI

4.1.19 Pharmacokinetics

PK assessments will be done on all subjects in the treatment-naive cohort and on up to 12 subjects in the previously treated cohort. Refer to the laboratory binder for instructions on collecting and processing these samples. Testing will be performed at the central clinical laboratory. CCI The PK sampling timepoints are provided in Table 2.

Table 2. 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 CCI

CCI

[redacted]

4.1.21 Extramedullary Disease Assessment

Pretreatment radiologic extramedullary disease assessment will be performed within 30 days before the first dose. A computed tomography (CT) scan with contrast (unless contraindicated) of the chest, abdomen, and pelvis and any other disease sites (e.g., neck) are required for the pretreatment extramedullary disease assessment for all subjects.

On-study extramedullary disease assessments will also be done by physical examination and laboratory results. Bone marrow and radiologic (as applicable) assessments are required for confirmation of CR per clinical guidelines (see Section 4.2). De-identified copies of all radiology results may be requested by the sponsor.

For subjects with baseline (screening) extramedullary disease, follow-up radiologic assessments are required at the end of Cycle 2 (±7 days), Cycle 4 (±7 days), and Cycle 6 (±7 days), then every 3 cycles (12 weeks, ±7 days) until Cycle 27, and then every 6 cycles thereafter or more frequently at investigator discretion. Subjects should have radiologic extramedullary disease 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. MRI may be used to evaluate non-target lesions that cannot be adequately imaged using CT (in cases where MRI is desirable, 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.

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.

In the event disease progression is suspected in subjects with baseline extramedullary disease, a CT scan must be performed. If the sole lesion lies within the field of prior radiotherapy, there must be evidence of disease progression in that lesion.

4.1.22 Study Drug Accountability

See Section 7.7.

4.1.23 Routine Clinical Assessments

Routine clinical assessments include physical examinations, recording of symptoms, and hematologic evaluations to evaluate for both AEs and assessment of disease progression at times when the CT scan is not obtained. If a subject shows signs of progression, the subject may continue treatment until progression is considered unequivocal progression by the investigator. 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 regardless of the administration of subsequent anticancer therapy.

4.2 Investigator's Assessment of Response to Treatment

The investigator must rate the subject's response to treatment per the Owen criteria (Owen 2013) and modified 3rd IWWM workshop criteria (Kimby 2006); see Table 3 and Table 5. Progression will be assessed by the Owen criteria (Owen 2013) and modified 3rd IWWM workshop criteria (Kimby 2006); see Table 4 and Table 6.

Overall response assessments will include evaluation of physical examinations, recording of symptoms, laboratory evaluations (Note: Serum immunoglobulins and serum M protein must be done within 7 days and bone marrow aspirate and biopsy [when applicable] must be done within 4 weeks of the contemporaneous radiologic evaluation), and radiologic evaluations per the schedule of assessments. Subjects who have signs and symptoms of progression outside of the scheduled assessment should be evaluated by the investigator with a physical examination and serum immunoglobulins and serum M protein to determine if disease progression is present. Additionally, any suspected case of disease progression should be assessed with a CT

scan for subjects with baseline extramedullary disease, and should be reported to the medical monitor. Subjects may continue study treatment until progression is confirmed by a serial examination (e.g., physical examination, serum immunoglobulins and serum M protein, or CT scan) at least 2 weeks later.

Table 3. Response Assessment Criteria for Waldenström Macroglobulinemia (Owen 2013)

Response	Definition
Complete response	• Absence of serum monoclonal IgM protein by immunofixation • Normal serum IgM level • Complete resolution of extramedullary disease, i.e., lymphadenopathy and splenomegaly if present at baseline • Morphologically normal bone marrow aspirate and trephine biopsy
Very good partial response	• Monoclonal IgM protein is detectable • ≥90% reduction in serum IgM level from baseline[a] • Complete resolution of extramedullary disease, i.e., lymphadenopathy/splenomegaly if present at baseline • No new signs or symptoms of active disease
Partial response	• Monoclonal IgM protein is detectable • ≥50% but <90% reduction in serum monoclonal IgM level from baseline [a] • Reduction in extramedullary disease i.e., lymphadenopathy/splenomegaly if present at baseline • No new signs or symptoms of active disease
Minor response	• Monoclonal IgM protein is detectable • ≥25% but <50% reduction in serum monoclonal IgM level from baseline [a] • No new signs or symptoms of active disease
Stable Disease	• Monoclonal IgM protein is detectable • <25% reduction and <25% increase in serum monoclonal IgM level from baseline [a] • No progression in extramedullary disease i.e., lymphadenopathy/splenomegaly • No new signs or symptoms of active disease

IgM=immunoglobin M
[a] Sequential changes in IgM levels may be determined either by M protein quantitation or total serum IgM quantitation by nephelometry.

Table 4. Progressive Disease Criteria for Waldenström Macroglobulinemia (Owen 2013)

Definition
• ≥25% increase in serum IgM level[a] with an absolute increase of at least 500 mg/dL from lowest nadir (requires confirmation on ≥2 consecutive measurements at least 4 weeks apart). AND/OR • Progression of clinical features attributable to the disease per Owen 2013.

IgM=immunoglobin M
[a] Sequential changes in IgM levels may be determined either by M protein quantitation or total serum IgM quantitation by nephelometry.

Table 5. Response Assessment for Waldenström Macroglobulinemia (Modified 3rd IWWM Workshop Criteria; Kimby 2006)

Response	Definition
Complete response	• Resolution of all symptoms • Normalization of serum IgM • Complete disappearance of IgM paraprotein by immunofixation • Resolution of any adenopathy or splenomegaly
Very good partial response	• ≥90% reduction in serum IgM level from baseline
Partial response	• ≥50% but <90% reduction in serum monoclonal IgM level from baseline[a]
Minor response	≥25% but <50% reduction in serum monoclonal IgM level from baseline[a]
Stable Disease	• <25% reduction and <25% increase in serum monoclonal IgM level from baseline[a] • Absence of new or increasing adenopathy or splenomegaly and/or other progressive signs or symptoms of WM.

IgM=immunoglobin M
[a] Sequential changes in IgM levels may be determined either by M protein quantitation or total serum IgM quantitation by nephelometry.

Table 6. Progressive Disease Criteria for Waldenström Macroglobulinemia (Modified 3rd IWWM Workshop Criteria; Kimby 2006)

Definition
• ≥25% increase in serum IgM level with an absolute increase of at least 500 mg/dL from lowest attained response value. Reconfirmation of the initial IgM increase is required when IgM is the sole criterion for progressive disease confirmation AND/OR • Progression of clinically significant disease-related symptom(s) AND/OR • Death from any cause or initiation of a new anti-neoplastic therapy will also be considered a progression event.

IgM=immunoglobin M

4.3 Treatment Termination and Safety Follow-Up Visits

A TT visit is required for safety assessments for any subjects who permanently discontinue study drug for any reason (except for death, loss to follow-up, or withdrawal of consent), including disease progression. The TT visit should be scheduled within 7 days of the last dose of study drug, if possible, and is not required for subjects who discontinue from study treatment within 10 days after a scheduled study visit.

In addition to the TT visit, each subject should be followed for SFU visit 30 days after his or her last dose of study drug to monitor for resolution or progression of AEs and to document the occurrence of any new events, regardless of whether the subject receives a new anticancer therapy or demonstrates disease progression within this timeframe. Subjects who withdraw consent for study treatment should still be encouraged to complete the SFU assessments before withdrawing consent, but these assessments cannot be mandated if subject consent for further study participation is withdrawn. If the TT visit and the SFU visit coincide, then these can be combined into 1 visit. The Schedule of Assessments (Appendix 4) describes the procedures required for the TT and SFU visits.

4.4 Follow-Up for Progression and Survival

Follow-Up after Study Treatment Discontinuation

Subjects who discontinue study treatment for reasons other than progressive disease (including subjects who discontinued due to AE and start use of alternative anticancer therapy) will be followed approximately every 3 months until disease progression. During this period, for subjects who require scans, the scans will be done every 3 months until 2 years, and then every 6 months thereafter until progression. Additionally, serum IgM and physical examinations will be collected every 6 months. Refer to Appendix 4 for the full list of assessments required during this period.

Long-Term Follow-Up

Once subjects progress—for all subjects who have not withdrawn consent—they will be contacted approximately every 3 months by clinic visit or telephone, to assess survival and the use of alternative anticancer therapy until death or loss to follow-up.

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.

5.2 Sample Size Considerations

Previously treated subjects: Simon's optimal 2-stage design

Response includes CR, very good partial response (VGPR), PR, or MR as defined in Section 5.5.3. This study will test the null hypothesis that the ORR is ≤35% against the alternative hypothesis that it is ≥55%. Using Simon's optimal 2-stage design, a total sample size of 76 subjects has 90% power to achieve a 1-sided significance level of 0.025. In Stage 1, 28 subjects will be evaluated for efficacy. If ≥12 out of 28 subjects (43%) achieve a response, then the study will continue to full enrollment. In Stage 2, a further 48 subjects will be enrolled. With Simon's optimal 2-stage design, an ORR of ≥46% (i.e., ≥35 subjects responding out of 76 subjects evaluated) will achieve a 1-sided significance level of ≤0.025.

Treatment-naive subjects: Exploratory cohort

No formal statistical tests of hypotheses will be performed. Eight to 12 evaluable subjects will be enrolled in this cohort for evaluation of preliminary efficacy and safety in this patient population.

5.3 Definition of Analysis Populations

The analysis population is defined as follows:

All-Treated Population: All enrolled subjects who receive ≥1 dose of study drug. The safety analyses and primary efficacy analyses will be performed on the All-treated population.

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

5.4 Missing Data Handling

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

5.5 Endpoint Data Analysis

5.5.1 Safety Analysis

Safety summaries will be included in the form of tables and listings. The frequency (number and percentage) of treatment-emergent AEs will be mapped using MedDRA and reported in each treatment group by MedDRA System Organ Class and Preferred Term. Summaries will also be presented by the severity of the AE (per CTCAE, v4.03 or higher) and by relationship to study drug. SAEs and AEs leading to study drug discontinuation will be summarized.

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

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

Figures of change from baseline will be generated to assess effect of acalabrutinib on peripheral T/B/NK cell counts and on serum immunoglobulin levels.

5.5.2 Demographics and Baseline Characteristics

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

5.5.3 Analysis of Efficacy Parameters

Efficacy parameters will be based on investigator assessment according to the response assessment criteria for WM (Owen 2013) and the modified 3rd IWWM workshop criteria (Kimby 2006). Efficacy parameters will be analyzed by the investigator. The co-primary endpoints are ORRs, defined as a subject achieving a MR or better according to the response assessment criteria for WM (Owen 2013) and by the modified 3rd IWWM workshop criteria (Kimby 2006), both as assessed by the investigator.

Overall Response Rate

ORR is defined as the proportion of subjects who achieve a CR, VGPR, PR, or MR. ORR will be calculated and the corresponding 95% 2-sided confidence interval will be derived.

Duration of Response

DOR is defined as the interval from the first documentation of CR, VGPR, PR, or MR to the earlier of the first documentation of definitive disease progression or death from any cause. Kaplan-Meier methods will be used to estimate event-free curves and corresponding quartiles (including the median). Data from surviving, non-progressing subjects will be censored at the earliest of the time of initiation of anticancer treatment or the last time that lack of WM progression was documented.

Progression-free Survival

PFS is defined as the interval from the start of acalabrutinib therapy to the earlier of the first documentation of disease progression (per Table 4) or death from any cause. Kaplan-Meier methods will be used to estimate the event-free curves and corresponding quartiles (including the median). Data from surviving, non-progressing subjects will be censored at the earlier of the time of initiation of anticancer treatment or the last time that lack of disease progression was documented.

Overall Survival

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

5.5.4 Analysis of Pharmacokinetic/CCI Parameters

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 “last” is the time of the last measurable C_t.

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

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

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

CCI

5.5.5 CCI

CCI

5.5.6 Patient-Reported Outcome

The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-30 will be used to assess health-related quality of life. The instrument will be scored, missing values handled, and standardized scores derived (ranging from 0–100) as recommended in the EORTC user manual. At each assessment point, absolute scores and changes from baseline will be calculated for each subscale, including core and overall total score. Tables and graphs will be generated to summarize the absolute scores and changes from baseline.

5.6 Interim Analysis

One formal interim analysis for futility with respect to ORR will be performed and documented. The formal documentation of the interim analysis will occur when subjects in Stage 1 (28 subjects) have been enrolled and have 8 weeks of evaluable response data for efficacy. However, should at any time ≥12 responses (MR or better) be observed among the 28 subjects enrolled, Stage 2 enrollment will continue without hold. Further enrollment of subjects into Stage 2 will be halted if there are <12 responders (MR+PR+VGPR+CR) observed among these 28 subjects. If there are at least 12 responders at the time the twenty-eighth subject has enrolled, screening for and enrollment into Stage 2 will not be halted as the minimum criteria for continuing enrollment will have been met.

In The Netherlands and France, enrollment in the exploratory cohort of subjects with treatment-naive WM will commence after efficacy has been confirmed in Stage 1 of the Simon's optimal 2-stage design.

5.7 Primary and Final Analysis

The primary analysis will occur when all subjects have completed Cycle 27 or have discontinued before Cycle 27.

The final analysis will occur after an approximate 5-year median follow-up period.

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.

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, 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 WM that were not present before the AE reporting period (see Section 6.2.1).
- Pre-existing medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.
- Abnormal laboratory values considered clinically significant by the investigator should be reported as an AE.

The following are NOT considered an AE:

- **Pre-existing condition that has not worsened**: A pre-existing condition (documented on the medical history CRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.
- **Preplanned hospitalization**: A hospitalization planned before signing the ICF is not considered an SAE, but rather a therapeutic intervention. However, if during the preplanned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before signing the ICF, will not be considered serious if they are performed after signing the ICF for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances are also not SAEs.
- **Diagnostic testing and procedures**: Testing and procedures should not be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported. If a test or procedure is done to rule out a diagnosis, the sign or

symptom leading to the test/procedure should be the event term, and the event term should only be updated to the diagnosis if/when the diagnosis is confirmed. Testing and procedures performed solely as screening measures (e.g., routine screening mammography or colonoscopy) should not be reported as AEs or SAEs.

- **Abnormal laboratory results that the investigator considers to not be clinically significant**: Abnormal laboratory results are not AEs unless they are clinically significant. For example, a clinically significant laboratory result is one that requires treatment (for example a blood transfusion for low hemoglobin) or requires a change in study drug (e.g., lowering the dose or withholding study drug while the laboratory finding resolves or stabilizes).

6.1.2 Serious Adverse Event

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

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

- It results in death (i.e., the AE actually causes or leads to death).
- It is life-threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death).
- It requires or prolongs in-patient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent 1 of the outcomes listed above).

6.1.3 Adverse Events of Special Interest

The following events are AEs of special interest (AESIs) for subjects who receive acalabrutinib and must be reported to the sponsor expeditiously (see Section 6.2.5 for reporting instructions), irrespective of regulatory seriousness criteria or causality:

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

6.1.4 Severity

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

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

6.1.5 Adverse Drug Reactions

For the purpose of reporting AEs and SAEs, see Section 6 of the Investigator Brochure, which contains the reference safety information.

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 CRF. All SAEs also must be reported on the SAE form (see Section 6.2.5).

6.2.1 Adverse Event Reporting Period

After the signing of the ICF and prior to the first dose of study drug, all SAEs must be reported. After the first dose of study drug, all AEs/SAEs, irrespective of attribution of causality, must be reported.

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

All SAEs that occur during the reporting period should be followed to resolution or until the investigator assesses the subject as stable, or until the subject is lost to follow-up or withdraws consent. Resolution/stable means the subject has returned to baseline state of health or the investigator does not expect any further improvement or worsening of the event.

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 test (e.g., 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 CRF and, when applicable, on an SAE form.

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 (e.g., 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?' Answer Yes or No.

See Appendix 2 for more detail on assessing causality.

6.2.3 Second Primary Malignancies

AEs for malignant tumors reported during a study should generally be assessed as SAEs. If no other seriousness criteria apply, the "Important Medical Event" criterion

should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a nonserious AE. For example, if the tumor is included as medical history and progression occurs during the study but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as nonserious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

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

6.2.4 Pregnancy

The investigator should report all pregnancies in study subjects and in the partners of study subjects within 24 hours using the Pregnancy Report Form. This form should be sent to the AstraZeneca Representative. Any pregnancy-associated SAE must be reported using the SAE report form, according to the usual timelines and directions for SAE reporting (Section 6.2.5).

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, wherein the estimated date of conception is determined to have occurred from the time of consent to 2 days after the last dose of study medication will be reported, followed to conclusion, and the outcome reported, as long as the subject or partner has consented to participate in follow-up.

Pregnancy itself is not regarded as an AE unless there is suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Likewise, elective abortions without complications are not

considered AEs. Any SAEs associated with pregnancy (e.g., congenital abnormalities/birth defects/spontaneous miscarriages or any other serious events) must additionally be reported as such using the SAE Form.

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

Upon completion of the pregnancy, additional information on the mother, pregnancy, and baby will be collected and sent to the AstraZeneca Representative.

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

All SAEs and AESIs must be reported within 24 hours of discovery. All initial SAE/AESI 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 sent to the AstraZeneca Representative. The AstraZeneca Representative may request follow-up and other additional information from the investigator (e.g., hospital admission/discharge notes and laboratory results).

Whenever possible, SAEs/AEs should be reported by diagnosis term not as a constellation of symptoms. Death due to disease progression should be recorded on the appropriate form in the electronic data capture system. If the primary cause of death is disease progression, the death due to disease progression should not be reported as an SAE. If the primary cause of death is something other than disease progression, then the death should be reported as an SAE with the primary cause of death as the event term, as death is typically the outcome of the event, not the event itself. The primary cause of death on the autopsy report should be the term reported. Autopsy and postmortem reports must be forwarded to the AstraZeneca Representative as outlined above.

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

An SAE may qualify for mandatory expedited reporting to regulatory authorities if the SAE is attributable to the investigational product (or if a causality assessment is not provided for the SAE, in which case a default of ‘related’ may be used for expedited reporting purposes) and the SAE is not listed in the current acalabrutinib Investigator

Brochure (i.e., an unexpected event). In this case, Acerta Pharma 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.

7.0 STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

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

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

7.1 Regulatory and Ethical Compliance

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

7.2 Institutional Review Board and Independent Ethics Committee

The investigator will submit this protocol, the ICF, Investigator Brochure, and any other relevant supporting information (e.g., all advertising materials) to the appropriate IRB/IEC for review and approval before study initiation. A signed protocol approval page; a letter confirming IRB/IEC approval of the protocol and informed consent; and a statement that the IRB/IEC is organized and operates according to Good Clinical Practices and the applicable laws and regulations; **must** be forwarded to Acerta Pharma **before** screening subjects for the study. Additionally, sites must forward a signed Food and Drug Administration (FDA) 1572 form (Statement of Investigator) to Acerta Pharma before screening subjects for study enrollment. Amendments to the protocol must also

be approved by the IRB/IEC and local regulatory agencies, as appropriate, before the implementation of changes in this study.

7.3 Informed Consent and Protected Subject Health Information Authorization

A copy of the IRB/IEC-approved ICF must be forwarded to Acerta Pharma for regulatory purposes. The investigator, or designee (designee must be listed on the Study Personnel Responsibility/Signature Log, see Section 7.12), **must** explain to each subject the purpose and nature of the study, the study procedures, the possible adverse effects, and all other elements of consent as defined in § 21 Code of Federal Regulations 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 ICF for a subject incapable of giving consent. Signed consent forms must remain in each subject's study file and be available for verification by study monitors at any time.

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

7.4 Subject Screening Log

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

7.5 Case Report Forms

Authorized study site personnel (see Section 7.12) will complete CRFs designed for this study according to the completion guidelines that will be provided. The investigator will ensure that the CRFs are accurate, complete, legible, and completed promptly. For record retention policies, refer to Section 7.8.

7.6 Study Monitoring Requirements

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

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

7.7 Investigational Study Drug Accountability

Acalabrutinib 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). If it is used, the Drug Re-Order Form (provided in the pharmacy binder) must also be included in the site's drug accountability records.

Contents of each shipment must be visually inspected to verify the quantity and to document the condition of study drug capsules. Following receipt of study drug, the

designated recipient completes and signs the CSSF. A copy of the signed and dated CSSF must be faxed or emailed to Acerta Pharma at the fax number/email address listed on the form; this completed form should be filed in the pharmacy binder.

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

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

At study initiation, the monitor will evaluate and approve the site's procedure for 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 FDA Form 1572, IRB/IEC approval letters, signed ICFs, drug accountability records, SAE forms transmitted to Acerta Pharma, subject files (source documentation) that substantiate entries in CRFs, 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. The amendment will be submitted to the IRB/IEC together with, if applicable, a revised model ICF. If the change in any way increases the risk to the subject or changes the scope of the study, then written documentation of IRB/IEC approval must be received by Acerta Pharma before the amendment may take effect. Additionally under this circumstance, information on the increased risk and/or change in scope must be provided to subjects already actively participating in the study, and they must read, understand, and sign any revised ICF confirming willingness to remain in the study.

7.10 Publication of Study Results

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

7.11 Clinical Study Insurance

Clinical study 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. CRF pages are completed promptly.
11. All Investigational New Drug Safety Reports and SUSAR Reports are submitted promptly to the IRB/IEC.
12. All SAEs are reported to the AstraZeneca Representative 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, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

As published in Am J Clin Oncol:

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

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

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

Appendix 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 (e.g., high dose, double strength) or as a “moderate CYP3A inhibitor” when another preparation was used (e.g., 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

		Cycle 1					Cycle 2		Cycle 3	Cycles 4 and 5	Cycles 6-12	Cycles 15, 18, 21, 24	Cycles 27-48	Cycles 48+[b]				
		Days (± 2)					Days (± 2)		Days (± 2)	Days (± 2)	Days (± 2)	Days (± 2)	Days (± 2)	Days (± 2)	TT Visit[c]	SFU Visit[c]	DFU[d]	LTFU[e]
	Screening[a]	1	8	15	22	28	15	28	28	28	28	28	28	28				
Informed consent	x																	
Confirm eligibility	x																	
Medical history	x																	
PE[f]/Vital signs[g]/Weight[f]	x	x	x	x	x	x	x	x	x	x	x	x	x	x (Q6C)	x	x	x	
ECOG status[h]	x	x	x	x	x	x	x	x	x	x	x	x	x	x (Q6C)	x	x		
ECG[i]	x														x	x		
Laboratory assessments:																		
Urine or serum pregnancy test[j]	x	x				x		x	x	x	x	x	x	x (Q6C)	x	x		
Hematology[k]	x	x[m]	x	x	x	x	x	x	x	x	x	x	x	x (Q6C)	x	x		
Serum chemistry[l]	x	x[m]	x	x	x	x	x	x	x	x	x	x	x	x (Q6C)	x	x		
Urinalysis[n]	x																	
T/B/NK cell count[o]		x[m]	x	x		x		x			C6 and C12 only	C18 & C24 only	Q6C starting at C27					
Serum Ig & M protein[p]	x			x		x		x	x	x	x	x	x	x (Q6C)	x	x	x	
HBV PCR[q]							x		x	x	QM	QM	QM	x (Q3M)			Q3M	Q3M
Bone marrow (aspirate and biopsy)[r]	x							x			C12 only and to confirm CR	Only to confirm CR	Only to confirm CR	Only to confirm CR				

		Cycle 1					Cycle 2		Cycle 3	Cycles 4 and 5	Cycles 6-12	Cycles 15, 18, 21, 24	Cycles 27-48	Cycles 48+[b]				
		Days (± 2)					Days (± 2)		Days (± 2)	Days (± 2)	Days (± 2)	Days (± 2)	Days (± 2)	Days (± 2)	TT Visit[c]	SFU Visit[c]	DFU[d]	LTFU[e]
	Screening[a]	1	8	15	22	28	15	28	28	28	28	28	28	28				
Radiologic assessment (as applicable) for extramedullary sites[r]	x							x		C4 only	Q3C and to confirm CR	Q3C and to confirm CR	Q6C and to confirm CR	Q6C and to confirm CR			x	
CCI		x[s]	x[s]			x[t]		x[t]							x[t]	x[t]		
Pharmacokinetics[u]		x	x	x	x	x												
Acalabrutinib dispensed		x	x	x	x	x	x	x	x	x	x	x	x	x (Q6C)				
Study drug compliance		x	x	x	x	x	x	x	x	x	x	x	x	x (Q6C)				
Response assessment[r]	x					x		x	x	x	x	x	x	x (Q6C)			x	
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x (Q6C)	x	x		
Adverse events[v]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PRO[w]	x							x		C4 only	C6, C9 & C12 only	x	x	x (Q6C)				
Survival Status																		x

AE=adverse event; C=cycle; CR=complete remission; DFU=discontinuation follow-up; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; ET=early termination; Ig=immunoglobulin; LTFU=long-term follow-up; PCR=polymerase chain reaction; PE=physical examination; PRO=patient-reported outcomes; Q3C=every 3 cycles; Q3M=every 3 months; Q6C=every 6 cycles; Q6M=every 6 months; QM=every month; SAE=serious adverse event; SFU=safety follow-up; TT=treatment termination.

Footnotes for ACE-WM-001 Schedule of Assessments:

a. Screening tests should be performed within 21 days before the first administration of study drug, unless otherwise indicated.
b. The end of study is defined as the last subject's last visit. Subjects who are deriving clinical benefit from acalabrutinib may continue on study until a rollover protocol is available.
c. A TT visit is required for subjects who permanently discontinue study drug early for any reason, including disease progression. A 30-day (+ 7 days) SFU visit after the last dose of study drug is required when subjects discontinue study drug. The TT visit should be scheduled within 7 days of the last dose of study drug, if possible, and is not required for subjects who discontinue from study treatment within 10 days after a scheduled study visit. Each subject should be followed until the SFU visit at 30 (+ 7) days after his or her last dose of study drug to monitor for resolution or progression of AEs 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.

d. Subjects who discontinue for reasons other than progressive disease (including subjects who discontinued due to AE and start use of alternative anticancer therapy) will be followed approximately Q3M until progressive disease. During this period, for subjects who require scans, scans will be done Q3M until 2 years, and then Q6M thereafter until progression. Additionally, serum IgM and physical examination will be collected.
e. Once subjects progress—for all subjects who have not withdrawn consent—they will be contacted approximately Q3M by clinic visit or telephone, to assess survival and the use of alternative anticancer therapy until death or loss to follow-up.
f. The screening physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. Symptom-directed physical examinations, including extramedullary disease assessments by palpation, will be done thereafter. Assessments will be made Q3C through Cycle 48, then Q6C thereafter.
g. Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has rested in the sitting position. Assessments will be made Q3C through Cycle 48, then Q6C thereafter.
h. ECOG assessments will be made Q3C through Cycle 48, then Q6C thereafter.
i. Subjects should be in supine position and resting for ≥ 10 minutes before study-related ECGs.
j. Women of childbearing potential only. 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. In general, assessments will be made Q3C through Cycle 48, then Q6C thereafter.
k. Hematology will include complete blood count with differential and platelet and reticulocyte counts. Cycle 1 Day 1 hematology does not need to be repeated if screening hematology was within 5 days. Assessments will be made Q3C through Cycle 48, then Q6C thereafter.
l. Serum chemistry will include albumin, alkaline phosphatase, bone-specific alkaline phosphatase, alanine transaminase, aspartate aminotransferase, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, c-terminal telopeptide, glucose, lactate dehydrogenase, magnesium, phosphate, 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. Assessments will be made Q3C through Cycle 48, then Q6C thereafter.
m. The indicated samples at this timepoint (Cycle 1 Day 1) must be drawn predose.
n. Urinalysis will include pH, ketones, specific gravity, bilirubin, protein, blood, and glucose.
o. T/B/NK cell count (i.e., CD3+, CD4+, CD8+, CD19+, CD16/56+). During Cycle 6 through Cycle 24, assessments will only be done at the end of Cycle 6, 12, 18, and 24. During Cycle 27 through Cycle 48, assessments will be done Q6C starting at Cycle 27. Assessments after Cycle 48 are not required.
p. Serum immunoglobulin will include IgG, IgM, IgA and Serum M protein. Starting at Cycle 6, IgG, IgM, IgA, and serum M protein will be done Q3C (12 weeks, ± 7 days) through Cycle 48, then Q6C thereafter.
q. Subjects who are hepatitis B core antibody positive (or have a known history of HBV infection) should be monitored monthly with a quantitative PCR test for HBV DNA. Assessments will be made QM from Cycle 6 to Cycle 48 or early discontinuation, and then Q3M thereafter. 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.
r Pretreatment extramedullary disease assessment including CT scan should be performed within 30 days before the first dose. A CT scan with contrast (unless contraindicated) of the chest, abdomen, and pelvis and any other disease sites (e.g., neck) are required for the pretreatment assessment. For subjects with baseline (screening) extramedullary disease, follow-up radiologic assessments are required at the end of Cycle 2 (±7 days), Cycle 4 (± 7 days), Cycle 6 (± 7 days), then every 3 cycles (12 weeks, ± 7 days) until Cycle 27, then every 6 cycles thereafter or more frequently at the investigator's discretion. At all other visits, extramedullary disease assessments will be done by physical examination and laboratory results. A bone marrow aspirate and biopsy will be done at screening or up to 60 days before the first dose of study drug. Bone marrow aspirate and biopsy are also required at end of Cycle 2 and Cycle 12, which must be done within 4 weeks of the contemporaneous radiologic evaluation. Furthermore, bone marrow and radiologic (as applicable) assessments are required for confirmation of complete remission. Pathologic review of the bone marrow aspirate and biopsy will be performed by a central laboratory (or local laboratory, if central laboratory is unavailable) for confirmation of WM diagnosis. CCI
s. CCI
t.

CCI

u. PK samples will be drawn per Table 2. This sampling will be limited to a subset of subjects as described in the protocol and timepoints are relative to the morning dose.
v. After the end of the protocol-defined AE reporting period (see Section 6.2.1), only SAEs considered related to study drug(s) or study procedures are required to be collected.
w. PRO assessment will be done at screening, at the end of Cycle 2, Cycle 4, and Cycle 6; and then Q6C thereafter until documentation of progressive disease or use of alternative anticancer therapy.

Appendix 5. Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

INTRODUCTION

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

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

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

DEFINITIONS

Potential Hy's Law

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

Hy's Law

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

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

IDENTIFICATION OF POTENTIAL HY'S LAW CASES

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

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

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

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

REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

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

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

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

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.

- If the alternative explanation is an AE/SAE, update the previously submitted PHL SAE accordingly with the new information (reassessing event term, causality, and seriousness criteria) following the sponsor's standard processes.

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

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

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

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

ACTIONS REQUIRED FOR REPEAT EPISODES OF POTENTIAL HY'S LAW

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

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

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

- <u>If the answer is **No**</u>**:**

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

- <u>If the answer is **Yes**</u>:

  Determine whether there has been a significant change in the subject's condition compared with the previous occurrence of PHL. Note: A "significant" change in the subject's condition refers to a clinically relevant change in any of the individual

liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator; this may be in consultation with the study medical monitor if there is any uncertainty.

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

LABORATORY TESTS

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

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

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

Reference

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

Appendix 6. Management of Study Procedures During Pandemic

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

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

If the subject is unable or unwilling to visit the study site due to COVID-19 related reasons, investigators may ask enrolled subjects to use healthcare facilities local to the subject to ensure safety and efficacy measures are done per protocol. If a study assessment is not done at either the site or a facility local to the subject, then its absence should be documented as a protocol deviation. Any protocol deviations resulting from the COVID-19 situation should be recorded and prefixed with COVID19.

STUDY SUBJECT PARTICIPATION

Conduct of Telephone Visits

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

Acalabrutinib Dose Modification Recommendation for COVID-19

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

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

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

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

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

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

Please contact the study medical monitor for further discussion.

Comparator Drugs or Drugs used in Combination with Acalabrutinib

- Please refer to guidance from the manufacturer.

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

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

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

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

COVID-19 SPECIFIC DATA ENTRY INSTRUCTIONS FOR INVESTIGATIONAL SITES

Adverse Event Recording

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

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

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

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

Study Treatment Recording

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

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

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

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

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

Capturing Telephone Contacts with Subjects

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

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

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

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

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

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

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