PROTOCOL

TITLE:	A Phase 2 Study of the Efficacy and Safety of ACP-196 in Subjects with Relapsed/Refractory CLL and Intolerant of Ibrutinib Therapy
PROTOCOL NUMBER:	ACE-CL-208
STUDY DRUG:	Acalabrutinib (ACP-196)
IND NUMBER:	118717
EUDRACT NUMBER:	2015-005317-68
SPONSOR MEDICAL MONITOR:	PPD PPD Phone: PPD Email: PPD
SPONSOR:	Acerta Pharma BV PPD 5349 AB Oss The Netherlands
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AMENDMENT 3 DATE:	Version 3.0 – 01 December 2017
AMENDMENT 4 DATE:	Version 4.0 – 24 February 2020
AMENDMENT 5 DATE:	Version 5.0 – 25 June 2020

Confidentiality Statement

PROTOCOL APPROVAL PAGE

Version 5.0

I have carefully read Protocol ACE-CL-208 entitled “A Phase 2 Study of the Efficacy and Safety of ACP-196 in Subjects with Relapsed/Refractory CLL and Intolerant of Ibrutinib Therapy”. I agree to conduct this study as outlined herein and in compliance with Good Clinical Practices (GCP) and all applicable regulatory requirements. Furthermore, I understand that the sponsor, Acerta Pharma, and the IRB/ IEC must approve any changes to the protocol in writing before implementation.

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

Principal Investigator’s Signature Date

Print Name

SUMMARY OF AMENDMENT 5.0

This protocol is being amended to clarify the definition of the end of the study and the time point for the final analysis.

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

Sections Impacted	Rationale
STUDY SYNOPSIS	Updated the Synopsis to reflect changes in the protocol.
Section 3.1 End of Study Section 3.7 Duration of Therapy Appendix 1 Schedule of Assessments (footnote "a")	The definition of the end of study has been changed to "the date of the last subject's last visit."
Section 3.1 End of Study	The time point for the final analysis was clarified to occur no earlier than the date the last subject has completed the end of Cycle 36 or has been withdrawn for any reason and completed the 30-day SFU visit (if applicable), whichever occurs first.
Section 3.9.2 Prohibited or Restricted Concomitant Therapies	Reference to Section 3.10.9 (dietary restrictions) was added to the paragraph on concomitant use of strong inhibitors/inducers of CYP3A, to alert to the prohibition of St John's wort, an herbal product that is also a strong CYP3A inducer described in the dietary restrictions section and listed in Appendix 4.

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ABBREVIATIONS

Abbreviation	Definition
ACP-196	acalabrutinib
AE	adverse event
ALC	absolute lymphocyte count
ANC	absolute neutrophil count
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
ASCO	American Society of Clinical Oncology
BID	twice per day (dosing)
BOR	best overall response
BTK	Bruton tyrosine kinase
BUN	blood urea nitrogen
CD	cluster of differentiation (cell surface marker)
cGMP	current Good Manufacturing Practice
CIRS-G	Cumulative Illness Rating Scale-Geriatric
CLL	chronic lymphocytic leukemia
CR	complete response (remission)
CrCL	creatinine clearance
CRF	case report form
CRi	complete remission with incomplete bone marrow recovery
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome p450
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	data monitoring committee
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EE	efficacy-evaluable (population)
EGFR	epidermal growth factor receptor
FDA	Food and Drug Administration
FISH	fluorescent in situ hybridization
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus

Abbreviation	Definition
HCV	hepatitis C virus
HR	hazard ratio
ICF	Informed Consent Form
IEC	independent ethics committee
IFNγ	interferon gamma
Ig	immunoglobulin
IRB	institutional review board
ITK	interleukin-2-inducible T-cell kinase
IV	intravenous
IVIG	intravenous immunoglobulins
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
K-M	Kaplan-Meier
LTFU	long-term follow-up
CCI	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NK	natural killer (cells)
nPR	nodular partial remission
ORR	overall response rate
OS	overall survival
PFS	progression-free survival
PCR	polymerase chain reaction
PD	pharmacodynamic
PK	pharmacokinetic
CCI	[redacted]
PML	progressive multifocal leukoencephalopathy
PR	partial response (remission)
QD	once per day (dosing)
QTc	corrected QT interval
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease or standard deviation
SFU	safety follow-up (visit)
SUSAR	suspected unexpected serious adverse reaction
TT	treatment termination (visit)
TTNT	time-to-next treatment

Abbreviation	Definition
TXK	tyrosine kinase
ULN	upper limit of normal
WHODRUG	World Health Organization Drug Dictionary

STUDY SYNOPSIS

Study Title:	A Phase 2 Study of the Efficacy and Safety of ACP-196 in Subjects with Relapsed/Refractory CLL and Intolerant of Ibrutinib Therapy
Protocol Number:	ACE-CL-208
Study Drug:	Acalabrutinib (also known as ACP-196)
Phase:	Phase 2
Comparator:	None
Study Centers:	Subjects were enrolled in approximately 50 centers globally.
Background and Rationale for Study	Chronic lymphocytic leukemia (CLL) is a malignancy of B cells that predominantly affects the older population. Chemoimmunotherapy, in particular the combination of purine analogs (e.g., fludarabine) with cyclophosphamide and rituximab, has become a standard for the treatment of young and/or fit individuals with CLL who require treatment. However, elderly subjects and those with comorbidities are often unable to tolerate combination chemoimmunotherapy regimens or experience inferior clinical outcomes when treated with these regimens. In addition, those subjects who have high-risk cytogenetics have inferior outcomes and may prove to be refractory to therapy and/or experience short remission durations and rapid progression of disease when treated with standard and currently available treatment regimens Bruton tyrosine kinase inhibition is an established therapeutic intervention for the treatment of CLL. Ibrutinib (IMBRUVICA®), a first-generation Bruton tyrosine kinase (BTK) inhibitor, has demonstrated efficacy in patients with relapsed or refractory CLL based on data from single-arm Phase 2 studies (PCYC 1102/1103) and the randomized Phase 3 study (RESONATE) (IMBRUVICA® [prescribing information]). Important safety risks have been observed with ibrutinib (see protocol). Chemical optimization, pharmacologic characterization, and toxicologic evaluation have led to identification of acalabrutinib, an orally administered, new chemical entity that covalently inhibits BTK and shows encouraging activity and acceptable safety in clinical and nonclinical studies. Within the class of BTK inhibitors, acalabrutinib is a more selective inhibitor of BTK than ibrutinib. An improved kinase selectivity profile for acalabrutinib may translate to pharmacologic benefits (see protocol)

	Acalabrutinib was specifically designed to be a more potent and selective inhibitor of BTK to avoid off-target side effects seen with other BTK inhibitors. When profiled against 395 human kinases, acalabrutinib was more selective than ibrutinib. In vitro and in vivo safety pharmacology studies with acalabrutinib have demonstrated a favorable nonclinical safety profile To date, no subjects have discontinued acalabrutinib due to reoccurrence of events that occurred with ibrutinib therapy. A better tolerated BTK inhibitor with fewer adverse events (AEs) has important efficacy implications. Recent studies have shown patients who require dose interruptions or discontinuation on ibrutinib therapy have poor outcomes, including increased progression events Recently emerging data report a median overall survival (OS) of 3 to 8 months for patients with relapsed/refractory CLL after discontinuation of ibrutinib treatment, including discontinuation due to AEs. In addition, patients with relapsed/refractory CLL who reduce their ibrutinib dosage (<420 mg daily) or miss ≥8 consecutive days of dosing experience shorter PFS. These results suggest a new unmet need has arisen to address therapeutic options for patients with relapsed/refractory CLL who are intolerant of ibrutinib, especially if they are not candidates for treatment or retreatment with purine analogue-based therapy. Thus an alternative BTK inhibitor—with a potentially distinct safety profile—may provide meaningful clinical benefit for relapsed/refractory patients with CLL who cannot, or can no longer, tolerate ibrutinib therapy, especially if purine analogue-based therapy is not an option.
Study Objectives:	**Primary Objective:** • Evaluate the efficacy of acalabrutinib in subjects with relapsed/refractory CLL who are intolerant of ibrutinib therapy **Secondary Objective:** • Evaluate the safety and tolerability of acalabrutinib in subjects with relapsed/refractory CLL who are intolerant of ibrutinib therapy **Exploratory Objectives:** CCI [redacted]

Study Design:	This is a multicenter, open-label, Phase 2 study evaluating the efficacy and safety of acalabrutinib in subjects with relapsed/refractory CLL (N=60) who are intolerant of ibrutinib therapy. For the purpose of this protocol, ibrutinib intolerant is defined as patients who cannot tolerate, or no longer can tolerate, ibrutinib therapy due to adverse reactions associated with treatment. Such patients may benefit from treatment with an alternative BTK inhibitor with a different safety profile than ibrutinib. Each treatment cycle will consist of 28 days (4 weeks). Radiologic tumor assessment will be done at screening, at the end of Cycles 3, 6, 9, 12, 18, 24, and then every year thereafter, while receiving acalabrutinib treatment. Confirmation of CR will require bone marrow analysis and radiologic tumor assessment. Safety evaluations will be done at every visit and will consist of assessment of AEs, physical examinations, and safety laboratory panels. Visits will be every 2 weeks for the first 2 cycles, then monthly through the end of Cycle 6, then every 3 cycles thereafter. Subjects who discontinue study drug for any reason other than disease progression will be followed for disease progression, regardless of whether the subject receives new anticancer treatment. A 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 study drug will have a safety follow-up (SFU) visit 30 (+7) days after the last dose of study drug. All endpoints in this study will be investigator assessed. Clinical sites will be used to collect and store computed tomography (CT) scan images. The end of study is defined as the date of the last subject's last visit. Subjects who are still on treatment at the time of the final study analysis and deriving clinical benefit from acalabrutinib treatment may continue treatment. At the time of the final data cutoff (DCO) 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. 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 6.2.5. 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.
Efficacy Endpoints:	Efficacy will be evaluated based on the modified International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 criteria The primary efficacy endpoint is overall response rate (ORR) assessed by the investigators. The secondary efficacy endpoints are: • Duration of response (DOR) • Progression-free survival (PFS) • Time-to-next treatment (TTNT) • Overall survival (OS)
Safety Endpoints:	The safety of acalabrutinib will be characterized by laboratory assessments and the type, frequency, severity, and causal attribution of AEs, or AEs leading to discontinuation of study treatment. For consistency of interpretation, AEs and laboratory results will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and the severity of both hematologic and nonhematologic AEs will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 or higher. Standard definitions for seriousness will be applied
CCI [redacted]	[redacted]
Sample Size:	Approximately 60 subjects.
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. Prior diagnosis of CLL that meets published diagnostic criteria as follows: a. Monoclonal B-cells (either kappa or lambda light chain restricted) that are clonally co-expressing ≥1 B-cell marker (CD19, CD20, or CD23) and CD5.

	b. Prolymphocytes may comprise ≤55% of blood lymphocytes. c. No evidence of cyclin D1 rearrangement or BCL-1 overexpression. d. Presence of ≥5 x 10^9 B lymphocytes/L (5000 µL) in the peripheral blood (at any point since diagnosis). 3. Must have received ≥1 prior therapy for CLL and not be appropriate for treatment or retreatment with purine analogue-based therapy as defined by ≥1 of the following criteria: a. Failure to respond (stable disease [SD] or disease progression on treatment) or progression-free interval of <3 years from treatment with a purine analogue-based therapy and anti-CD20 antibody-containing chemoimmunotherapy regimen after ≥2 cycles. b. Age ≥70 years c. Age ≥65 years with the presence of 1 of the following comorbidities that might place the subject at an unacceptable risk for treatment-related toxicity with purine analogue-based therapy, provided they have received ≥1 prior treatment including ≥2 cycles of an alkylating-agent based (or purine analogue-based) anti-CD20 antibody-containing chemoimmunotherapy regimen: i. Cumulative Illness Rating Scale-Geriatric (CIRS-G; see protocol) ≥6. ii. Creatinine clearance (CrCL) <70 mL/min. d. History of purine analogue-associated autoimmune anemia, neutropenia, or autoimmune thrombocytopenia. e. Fluorescent in situ hybridization (FISH) showing 17p deletion mutation or p53 mutation (by central laboratory). 4. Intolerant of ibrutinib, defined as: a. The subject has discontinued ibrutinib therapy due to Grade 3 or 4 AEs that persisted in spite of optimal supportive care measures **OR** b. Subjects who had Grade 2 AEs related to ibrutinib therapy, in spite of optimal supportive care measures that persisted for ≥2 weeks or that recurred ≥2 times whether dose was reduced or discontinued. 5. Measurable nodal disease by CT, defined as ≥1 lymph node >1.5 cm as measured in the longest diameter in a site that has not been previously irradiated. An irradiated lesion may be assessed for measurable disease only if there has been documented progression in that lesion since radiotherapy has ended. 6. Documented disease progression after stopping ibrutinib therapy as defined by the IWCLL 2008 criteria (see protocol).

	7. Eastern Cooperative Oncology Group (ECOG) performance status of ≤2. 8. Women who are sexually active and can bear children must agree to use highly effective forms of contraception during the study and for 2 days after the last dose of acalabrutinib. Highly effective forms of contraception are defined in the protocol. 9. This criterion has been removed as of Protocol Amendment 3. 10. This criterion has been removed as of Protocol Amendment 3. 11. Willing and able to participate in all required evaluations and procedures in this study protocol including, swallowing capsules without difficulty. 12. 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:	Subjects will be ineligible for this study if they meet **any** of the following criteria: 1. Ongoing Grade 3 or 4 AE attributed to ibrutinib therapy. Note: Subjects may be eligible for enrollment once the ibrutinib-related AE improves to Grade ≤2. 2. Treatment with systemic anticancer therapy for CLL is prohibited between discontinuation of ibrutinib and enrollment on this trial. 3. Prior exposure to a BCL-2 inhibitor (e.g., venetoclax/ABT-199). 4. Prior malignancy (other than CLL), except for adequately treated basal cell or squamous cell skin cancer, in situ cancer, or other cancer from which the subject has been disease free for ≥2 years. 5. Significant cardiovascular disease such as uncontrolled or symptomatic untreated 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 at screening. Exception: Subjects with controlled, asymptomatic atrial fibrillation during screening are allowed to enroll on study. 6. Malabsorption syndrome, disease significantly affecting gastrointestinal function, resection of the stomach, extensive small bowel resection that is likely to affect absorption, symptomatic inflammatory bowel disease, partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass. 7. Evidence of active Richter's transformation or any evidence of disease progression on ibrutinib therapy or any BTK inhibitor.

	8. CNS involvement by CLL or related Richter's transformation. 9. Known history of human immunodeficiency virus (HIV), serologic status reflecting active hepatitis B or C infection, or any uncontrolled active systemic infection. a) Subjects who are hepatitis B core antibody (anti-HBc) positive and who are surface antigen negative will need to have a negative polymerase chain reaction (PCR) result before enrollment. Those who are hepatitis B surface antigen (HBsAg) positive or hepatitis B PCR positive will be excluded. b) Subjects who are hepatitis C antibody positive will need to have a negative PCR result before enrollment. Those who are hepatitis C PCR positive will be excluded. 10. Uncontrolled autoimmune hemolytic anemia (AIHA) or idiopathic thrombocytopenic purpura (ITP) defined as declining hemoglobin or platelet count secondary to autoimmune destruction within the screening period or requirement for high doses of steroids (>20 mg daily of prednisone or equivalent for longer than 2 weeks). 11. History of stroke or intracranial hemorrhage within 2 months before the first dose of study drug. 12. History of bleeding diathesis (e.g., hemophilia or von Willebrand disease). 13. Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before screening. 14. Major surgical procedure within 28 days of first dose of study drug. Note: If a subject had major surgery, they must have recovered adequately from any toxicity and/or complications from the intervention before the first dose of study drug. 15. Requires treatment with a strong CYP3A inhibitor 16. Requires treatment with proton-pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). Subjects receiving proton-pump inhibitors who switch to H2-receptor antagonists or antacids are eligible for enrollment to this study. 17. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon). 18. Absolute neutrophil count (ANC) $<0.75 \times 10^9$/L or platelet count $<50 \times 10^9$/L, unless there is bone marrow involvement. 19. Total bilirubin >1.5 x upper limit of normal (ULN); or AST or ALT >3.0 x ULN. 20. Estimated CrCL of <30 mL/min, calculated using the formula of Cockcroft and Gault [(140-Age) • Mass (kg)/(72 • creatinine mg/dL) • multiply by 0.85 if female] 21. Breastfeeding or pregnant.

	22. Concurrent participation in another therapeutic clinical trial.
Dose Regimen/Route of Administration:	Acalabrutinib 100 mg is intended to be administered orally twice per day (BID) with 8 ounces (approximately 240 mL) of water. Doses should be administered 12 hours apart (a window of ±1 hour is allowed). The capsules should be swallowed intact. Subjects should not attempt to open capsules or dissolve them in water.
Concomitant Medications:	**<u>Permitted Concomitant Therapy</u>** Antiemetics are permitted if clinically indicated. Standard supportive care medications are permitted as per institutional standards. Use of hematopoietic growth factors is permitted per the American Society of Clinical Oncology (ASCO) guidelines. **<u>Prohibited or Restricted Concomitant Therapy</u>** Any chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy for treating CLL are prohibited if being used to treat the disease initially under study. High-dose corticosteroids used to treat underlying CLL 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. The concomitant use of strong inhibitors/inducers of CYP3A (see protocol) should be avoided when possible (see protocol). If a subject requires short-term treatment with a strong CYP3A inhibitor (i.e., anti-infectives for up to 7 days), interrupt acalabrutinib treatment. Avoid coadministration of strong CYP3A inducers. If a subject requires treatment with a strong CYP3A inducer, increase the acalabrutinib dose to 200 mg BID during concomitant administration with the strong inducer and return to recommended dose of 100 mg BID after stopping the strong CYP3A inducer. For additional information on drugs with potential drug-drug interactions, refer to protocol.
Safety Plan	This trial will be monitored in accordance with the sponsor's pharmacovigilance procedures. AEs and SAEs will be reviewed internally as part of ongoing safety surveillance. Quarterly conference calls with the investigators and applicable site staff will be conducted to discuss study progress, obtain investigator feedback and exchange, and discuss "significant safety events" (i.e., AEs leading to dose reductions, related SAEs, and deaths). In addition, an independent data monitoring committee (DMC) will be formed to review data for subject safety. Data review will be

	focused on, but not limited to deaths, treatment discontinuations, SAEs, and Grade 3/4 AEs, as well as special events of interest. After review of data, the DMC will provide recommendations regarding stopping or continuing the study in accordance with the DMC charter. The DMC will meet approximately when the first 15 subjects have been treated through Week 8, 30 subjects have been treated through Week 8, and subsequently every year, as needed, until the final DCO and database closure for the study. Additional meetings may be scheduled at the request of the DMC or the sponsor.
Statistical Methods:	The statistical methods presented in this section provide a high-level summary of analysis to be performed for this study. Detailed analyses will be described in the Statistical Analysis Plan (SAP). The SAP will be finalized before database lock. Any changes to the methods described in the final SAP will be justified and described in the clinical study report. No interim analysis is planned for this study. The primary analysis will be performed after all subjects have completed the study. Continuous variables will be summarized by number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by the number of subjects and percentage in each category. **Statistical Basis for the Sample Size** The primary objective of this study is to determine the ORR as assessed by investigators according to modified IWCLL criteria. A target true ORR rate of 40% is believed to be clinically meaningful in this difficult-to-treat population with limited alternative treatment options. With a total of 60 subjects, the 95% confidence interval for various observed ORR values are provided in the protocol. This provides reasonable precision for estimating ORR in this target patient population. Finally, the probability of observing one or more instances of an AE with a background rate of 1%, 2%, 5%, and 10% in 60 subjects is 45.3%, 70.2%, 95.4%, and 99.8%, respectively.

1.0 BACKGROUND INFORMATION

1.1 CHRONIC LYMPHOCYTIC LEUKEMIA

Chronic lymphocytic leukemia (CLL) is a malignancy of B cells that predominantly affects the older population. Chemoimmunotherapy, in particular the combination of purine analogs (e.g., fludarabine) with cyclophosphamide and rituximab, has become a standard for the treatment of young and/or fit individuals with CLL who require treatment. However, elderly subjects and those with comorbidities are often unable to tolerate combination chemoimmunotherapy regimens or experience inferior clinical outcomes when treated with these regimens. In addition, those subjects who have high-risk cytogenetics have inferior outcomes and may prove to be refractory to therapy and/or experience short remission durations and rapid progression of disease when treated with standard and currently available treatment regimens (Hallek 2010, Hillmen 2007).

1.2 BRUTON TYROSINE KINASE INHIBITION IN CLL

Bruton tyrosine kinase (BTK) inhibition is an established therapeutic intervention for the treatment of CLL. Ibrutinib (IMBRUVICA®), a first-generation BTK inhibitor, has demonstrated efficacy in patients with relapsed or refractory CLL based on data from single-arm Phase 2 studies (PCYC 1102/1103) and the randomized Phase 3 study (RESONATE) (IMBRUVICA® [prescribing information]). In the RESONATE study, which had a median follow-up of 9.4 months, ibrutinib demonstrated clinically and statistically significant improvement over ofatumumab in progression-free survival (PFS) (hazard ratio [HR]=0.22), overall survival (OS) (HR=0.43) and ORR (42.6% versus 4.1% by independent assessment and 69.7% versus 21.4% by investigator assessment).

Important safety risks observed with ibrutinib include the following adverse reactions (IMBRUVICA® [prescribing information]):

- Fatal bleeding events have occurred in patients treated with ibrutinib. Major hemorrhage (≥ Grade 3, serious, or any central nervous system events; e.g., intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post-procedural hemorrhage) have occurred in 4% of patients, with fatalities occurring in 0.4% of patients.

- Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with ibrutinib therapy. Grade ≥3 infections have occurred in 24% of patients.

- Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (23%), thrombocytopenia (8%), and anemia (3%) based on laboratory measurements occurred in patients with B-cell malignancies.
- Fatal and serious cardiac arrhythmias have occurred with ibrutinib therapy. Grade 3 or greater ventricular tachyarrhythmias occurred in 0.2% of patients, and Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4% of patients.
- Hypertension of any grade occurred in 12% of patients treated with ibrutinib in clinical trials. Grade 3 or greater hypertension occurred in 5% of patients.
- Other malignancies (10%) including non-skin carcinomas (4%) have occurred in patients treated with ibrutinib in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (6%).
- Tumor lysis syndrome (TLS) has been infrequently reported with ibrutinib therapy.
- Based on findings in animals, ibrutinib can cause fetal harm when administered to a pregnant woman. Administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis caused embryofetal toxicity including malformations at exposures that were 2 to 20 times higher than those reported in patients with hematologic malignancies.

Chemical optimization, pharmacologic characterization, and toxicologic evaluation have led to identification of acalabrutinib, an orally administered, new chemical entity that covalently inhibits BTK and shows encouraging activity and acceptable safety in clinical and nonclinical studies. Within the class of BTK inhibitors, acalabrutinib is a more selective inhibitor of BTK than ibrutinib. An improved kinase selectivity profile for acalabrutinib may translate to pharmacologic benefits as outlined below:

- Ibrutinib is a potent covalent inhibitor of epidermal growth factor receptor (EGFR); acalabrutinib is not (Covey 2015).
- Ibrutinib is associated with clinically significant bleeding events in patients including intracranial hemorrhage. The mechanism for the bleeding events is not well understood. However, ibrutinib impairs thrombus formation in an in vivo model at physiologically relevant concentrations; acalabrutinib does not (Covey 2015).
- Ibrutinib is a potent covalent inhibitor of interleukin-2-inducible T-cell kinase (ITK). As such, ibrutinib interferes with natural killer (NK) cell-mediated function and antitumor activities of therapeutic CD20 antibodies (Da Roit 2015). Acalabrutinib does not inhibit ITK. Consequently in vitro studies show no effect of acalabrutinib on NK cell function or antitumor activities of therapeutic CD20 antibodies (Rajasekaran 2014).

- Ibrutinib is also a potent covalent inhibitor of tyrosine kinase (TXK). ITK and TXK regulate the development of cytotoxic $CD8^+$ T cells (Atherly 2006) and modulate interferon gamma (IFNγ) release (Takeba 2002). Acalabrutinib is not a potent inhibitor of TXK. In vivo tumor models show robust expansion of $CD8^+$ T cells with acalabrutinib treatment compared with ibrutinib (Lannutti 2015). In vitro T-cell studies show reduced $CD8^+$ T-cell viability with ibrutinib treatment compared with acalabrutinib (Covey 2015). Recently conducted in vitro $CD8^+$ T-cell functional assays show ibrutinib negatively impacts T-cell function (i.e., cytotoxicity and IFNγ release), while acalabrutinib does not. The differential potency of acalabrutinib versus ibrutinib on key modulators of T-cell function may lead to better clinical outcomes in patients, such as a reduced incidence of infections with acalabrutinib treatment.

1.3 ACALABRUTINIB

CCI [redacted]

CCI [redacted]

Acalabrutinib is orally administered in humans and is suitable for formulating in capsules. For clinical testing, acalabrutinib has been manufactured and formulated according to current Good Manufacturing Practices (cGMP).

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

1.3.1 Mechanism of Action

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

1.3.2 Safety Pharmacology

In vitro and in vivo safety pharmacology studies with acalabrutinib have demonstrated a favorable nonclinical safety profile; for detailed information on the safety pharmacology of acalabrutinib, refer to the Acalabrutinib Investigator Brochure.

1.3.3 Drug-Drug Interaction Potential

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

Please refer to Section 3.10.10 for guidance on drugs that may cause drug-drug interactions.

1.4 CLINICAL EXPERIENCE – ACALABRUTINIB

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

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

Subjects with relapsed CLL have been evaluated for tumor response based on modified International Working Group response criteria (Hallek 2008) as recently updated (Cheson 2012) to include partial response (PR) with treatment-induced lymphocytosis. Few subjects have had disease progression and no Richter's transformation has been observed in these subjects.

To date, no subjects have discontinued acalabrutinib due to reoccurrence of events that occurred with ibrutinib therapy. A better tolerated BTK inhibitor with fewer AEs has important efficacy implications. Recent studies have shown patients who require dose interruptions or discontinuation on ibrutinib therapy have poor outcomes, including increased progression events (Barr 2015). For more detailed, up-to-date information, refer to the Acalabrutinib Investigator Brochure.

1.5 BENEFIT/RISK

Acalabrutinib is a potent, orally administered small-molecule inhibitor of BTK. In the Phase 1/2 study of acalabrutinib in subjects with CLL, no dose-limiting toxicities (DLTs) have been identified at dosages of ≤400 mg once per day (QD) or 100 to 200 mg twice per day (BID). The ORR in the evaluable subjects for this study is 94% with some subjects obtaining PRs after only 2 cycles of therapy. In summary, the preliminary data suggest that acalabrutinib is well tolerated and has robust activity as a single agent in the treatment of subjects with relapsed or refractory CLL, including those with 17p del or

11q del. In addition, pharmacodynamic (PD) results show the 100-mg BID regimen produces optimal target coverage over 24 hours (i.e., more complete coverage of de novo synthesis of BTK), which may provide greater clinical benefit than the QD regimen of ibrutinib.

Recently emerging data report a median OS of 3 to 8 months for patients with relapsed/refractory CLL after discontinuation of ibrutinib treatment, including discontinuation due to adverse events (AEs) (Jain 2015, Maddocks 2015, Pinilla-Ibarz 2015). In addition, patients with relapsed/refractory CLL who reduce their ibrutinib dosage (<420 mg daily) or miss ≥8 consecutive days of dosing experience shorter PFS (Barr 2015). These results suggest a new unmet need has arisen to address therapeutic options for patients with relapsed/refractory CLL who are intolerant of ibrutinib, especially if they are not candidates for treatment or retreatment with purine analogue-based therapy. For this subset of patients, the recommended therapy is idelalisib plus rituximab per National Comprehensive Cancer Network (NCCN) guidelines (NCCN 2015). However, little, if any, clinical data have been reported for patients who receive idelalisib therapy after ibrutinib discontinuation. In fact, the idelalisib Phase 3 registration study excluded patients previously treated with ibrutinib. Thus, the quality and duration of objective responses in patients who receive idelalisib in the post-ibrutinib setting is unknown. In addition, the reported Phase 2 and Phase 3 PFS results for ibrutinib therapy (Byrd 2014a, Byrd 2014b) in patients with relapsed/refractory CLL are consistently suggestive of a longer median PFS than reported for idelalisib plus rituximab therapy (Sharman 2014). Just as importantly, idelalisib therapy is also associated with serious risks of hepatotoxicity, colitis, pneumonitis, and intestinal perforation (ZYDELIG® prescribing information); none of which have been associated with either ibrutinib or acalabrutinib therapy. Other treatment options for this subset of patients include anti-CD20 antibody monotherapy (NCCN 2015), though the Phase 3 studies for ibrutinib and idelalisib showed minimal clinical activity of single-agent ofatumumab or rituximab, respectively, in relapsed/refractory CLL (Byrd 2014b, Furman 2014). Thus an alternative BTK inhibitor—with a potentially distinct safety profile—may provide meaningful clinical benefit for relapsed/refractory patients with CLL who cannot, or can no longer, tolerate ibrutinib therapy, especially if purine analogue-based therapy is not an option.

2.0 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE:

- Evaluate the efficacy of acalabrutinib in subjects with relapsed/refractory CLL who are intolerant of ibrutinib therapy

2.2 SECONDARY OBJECTIVE:

- Evaluate the safety and tolerability of acalabrutinib in subjects with relapsed/refractory CLL who are intolerant of ibrutinib therapy

2.3 EXPLORATORY OBJECTIVES:

CCI [redacted]

3.0 STUDY DESIGN

This is a multicenter, open-label, Phase 2 study evaluating the efficacy and safety of acalabrutinib in subjects with relapsed/refractory CLL (N=60) who are intolerant of ibrutinib therapy. For the purpose of this protocol, ibrutinib intolerant is defined as patients who cannot tolerate, or no longer can tolerate, ibrutinib therapy due to adverse reactions associated with treatment. Such patients may benefit from treatment with an alternative BTK inhibitor with a different safety profile than ibrutinib.

Subjects will be considered ibrutinib intolerant (at any dose/or duration) if they have discontinued ibrutinib therapy due to Grade 3 or 4 AEs that persisted in spite of optimal supportive care measures (for example atrial fibrillation/flutter, cardiac arrhythmia, diarrhea, rash, ecchymosis, myalgia or arthralgia), or if subjects had Grade 2 AEs related to ibrutinib therapy, in spite of optimal supportive care measures, that persisted for ≥2 weeks or that recurred ≥2 times, whether dose was reduced or discontinued. Subjects will be treated with acalabrutinib 100 mg BID. Treatment may be continued until disease progression or an unacceptable drug-related toxicity occurs.

Each treatment cycle will consist of 28 days (4 weeks). Radiologic tumor assessments will be done at screening, at the end of Cycles 3, 6, 9, 12, 18, 24, and then every year thereafter, while receiving acalabrutinib treatment. Confirmation of complete response (CR) will require bone marrow analysis and radiologic tumor assessment. Safety evaluations will be done at every visit and will consist of assessment of AEs, physical

examinations, and safety laboratory panels. Visits will be every 2 weeks for the first 2 cycles, then monthly through the end of Cycle 6, then every 3 cycles thereafter. Subjects who discontinue study drug for any reason other than disease progression will be followed for disease progression, regardless of whether the subject receives new anticancer treatment. A 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 study drug will have a safety follow-up (SFU) visit 30 (+7) days after the last dose of study drug.

All endpoints in this study will be investigator assessed. Clinical sites will be used to collect and store computed tomography (CT) scan images.

Refer to Appendix 1 for a comprehensive list of study assessments and their timing.

3.1 END OF STUDY

The final analysis will take place no earlier than the date the last subject has completed the end of Cycle 36 or has been withdrawn for any reason and completed the 30-day SFU visit (if applicable), whichever occurs first.

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

Subjects who are still on treatment at the time of the final study analysis and deriving clinical benefit from acalabrutinib treatment may continue treatment. At the time of the final data cutoff (DCO) 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. All active subjects are eligible to continue to receive acalabrutinib after database closure. There will be no further data collection other than reporting of serious adverse events (SAEs) per Section 6.2.5. 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

3.2.1 Efficacy Endpoints

Efficacy will be evaluated based on the modified International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 criteria (Appendix 2).

The primary efficacy endpoint is ORR assessed by the investigators.

The secondary efficacy endpoints are:

- Duration of response (DOR)
- PFS
- Time-to-next treatment (TTNT)
- OS

3.2.2 Safety Endpoints

The safety of acalabrutinib will be characterized by laboratory assessments and the type, frequency, severity, and causal attribution of AEs, or AEs leading to discontinuation of study treatment.

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

3.2.3 CCI

CCI

3.3 RATIONALE FOR STUDY DESIGN AND DOSING REGIMEN

3.3.1 Dose Selection Rationale

As described in Section 1.4, acalabrutinib is currently being evaluated in a Phase 1/2 study in subjects with CLL, Richter's syndrome, or prolymphocytic leukemia

(ACE-CL-001). In this study, subjects have received oral dosages of 100 to 400 mg QD and 100 to 200 mg BID of acalabrutinib. All tested dose levels have been well tolerated. No DLT has occurred at any dose level, and the MTD was not reached. PD results from this study also show 100 and 200 mg BID have the highest BTK occupancy at 24 hours of all the regimens evaluated. Robust clinical responses have been observed. Therefore, based on pharmacokinetic (PK)/PD and efficacy results of ACE-CL-001, acalabrutinib 100 mg BID will be evaluated in this study.

3.3.2 Selection of the Patient Population

As discussed in Section 1.5, patients with relapsed/refractory CLL who discontinue ibrutinib due to AEs or who reduce their ibrutinib dosage or miss ≥8 consecutive days of dosing experience poor clinical outcomes (OS and PFS). Treatment options are limited for these patients with relapsed/refractory CLL who are intolerant to ibrutinib and not considered appropriate candidates for purine analogue-based therapy. Per NCCN guidelines (NCCN 2015), the preferred therapy for this subset of patients after ibrutinib is idelalisib plus rituximab. However, as stated in Section 1.5, no significant data exist on ORR or PFS in patients treated with idelalisib after ibrutinib therapy because the Phase 3 idelalisib study excluded patients with previous exposure to ibrutinib.

In addition, the reported Phase 2 and Phase 3 PFS results for ibrutinib therapy (Byrd 2014a, Byrd 2014b) in patients with relapsed/refractory CLL are consistently suggestive of a longer median PFS than reported for idelalisib + rituximab therapy (Sharman 2014). Per NCCN guidelines (NCCN 2015), monotherapy with anti-CD20 antibodies is listed as a potential treatment option for this population. However, the recent results from the ibrutinib and idelalisib Phase 3 studies show monotherapy with anti-CD20 antibodies has minimal clinical activity in relapsed/refractory CLL (Byrd 2014b, Furman 2014). In other words, this protocol is designed to assess the efficacy and safety of a second-generation BTK inhibitor in patients who cannot, or can no longer, tolerate ibrutinib therapy and have few alternative treatment options.

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. Prior diagnosis of CLL that meets published diagnostic criteria (Hallek 2008) as follows:
    a. Monoclonal B cells (either kappa or lambda light chain restricted) that are clonally co-expressing ≥1 B-cell marker (CD19, CD20, or CD23) and CD5.
    b. Prolymphocytes may comprise ≤55% of blood lymphocytes.
    c. No evidence of cyclin D1 rearrangement or BCL-1 overexpression.
    d. Presence of ≥5 x 10^9 B lymphocytes/L (5000 µL) in the peripheral blood (at any point since diagnosis).
3. Must have received ≥1 prior therapy for CLL and not be appropriate for treatment or retreatment with purine analogue-based therapy as defined by ≥1 of the following criteria:
    a. Failure to respond (stable disease [SD] or disease progression on treatment) or progression-free interval of <3 years from treatment with a purine analogue-based therapy and anti-CD20 antibody–containing chemoimmunotherapy regimen after ≥2 cycles.
    b. Age ≥70 years
    c. Age ≥65 years with the presence of 1 of the following comorbidities that might place the subject at an unacceptable risk for treatment-related toxicity with purine analogue-based therapy, provided they have received ≥1 prior treatment including ≥2 cycles of an alkylating-agent based (or purine analogue-based) anti-CD20 antibody-containing chemoimmunotherapy regimen:
        i. Cumulative Illness Rating Scale - Geriatric (CIRS-G) (Appendix 3) ≥6.
        ii. Creatine clearance (CrCL) <70 mL/min.
    d. History of purine analogue-associated autoimmune anemia, neutropenia, or autoimmune thrombocytopenia.
    e. Fluorescent in situ hybridization (FISH) showing 17p deletion mutation or p53 mutation (by central laboratory).
4. Intolerant of ibrutinib, defined as:
    a. The subject has discontinued ibrutinib therapy due to Grade 3 or 4 AEs that persisted in spite of optimal supportive care measures **OR**
    b. Subjects who had Grade 2 AEs related to ibrutinib therapy, in spite of optimal supportive care measures that persisted for ≥2 weeks or that recurred ≥2 times whether dose was reduced or discontinued.
5. Measurable nodal disease by CT defined as ≥1 lymph node >1.5 cm as measured in the longest diameter in a site that has not been previously irradiated. An irradiated lesion may be assessed for measurable disease only if there has been documented progression in that lesion since radiotherapy has ended.
6. Documented disease progression after stopping ibrutinib therapy as defined by the IWCLL 2008 criteria (Appendix 2).
7. Eastern Cooperative Oncology Group (ECOG) performance status of ≤2.

8. Women who are sexually active and can bear children must agree to use highly effective forms of contraception during the study and for 2 days after the last dose of acalabrutinib. Highly effective forms of contraception are defined in Section 3.10.11.
9. This criterion has been removed as of Protocol Amendment 3.
10. This criterion has been removed as of Protocol Amendment 3.
11. Willing and able to participate in all required evaluations and procedures in this study protocol, including swallowing capsules without difficulty.
12. 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. Ongoing Grade 3 or 4 AE attributed to ibrutinib therapy. Note: Subjects may be eligible for enrollment once the ibrutinib-related AE improves to Grade ≤2.
2. Treatment with systemic anticancer therapy for CLL is prohibited between discontinuation of ibrutinib and enrollment on this trial.
3. Prior exposure to a BCL-2 inhibitor (e.g., venetoclax/ABT-199).
4. Prior malignancy (other than CLL), except for adequately treated basal cell or squamous cell skin cancer, in situ cancer, or other cancer from which the subject has been disease free for ≥2 years.
5. Significant cardiovascular disease such as uncontrolled or symptomatic untreated 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 at screening. Exception: Subjects with controlled, asymptomatic atrial fibrillation during screening are allowed to enroll on study.
6. Malabsorption syndrome, disease significantly affecting gastrointestinal function, resection of the stomach, extensive small bowel resection that is likely to affect absorption, symptomatic inflammatory bowel disease, partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass.
7. Evidence of active Richter's transformation or any evidence of disease progression on ibrutinib therapy or any BTK inhibitor.
8. CNS involvement by CLL or related Richter’s transformation.
9. Known history of HIV, serologic status reflecting active hepatitis B or C infection, or any uncontrolled active systemic infection.
    a) Subjects who are anti-hepatitis B core antibody (anti-HBc) positive and who are surface antigen negative will need to have a negative polymerase chain reaction (PCR) result before enrollment. Those who are hepatitis B surface antigen (HBsAg) positive or hepatitis B PCR positive will be excluded.
    b) Subjects who are hepatitis C antibody positive will need to have a negative PCR result before enrollment. Those who are hepatitis C PCR positive will be excluded.

10. Uncontrolled autoimmune hemolytic anemia (AIHA) or idiopathic thrombocytopenic purpura (ITP) defined as declining hemoglobin or platelet count secondary to autoimmune destruction within the screening period or requirement for high doses of steroids (>20 mg daily of prednisone or equivalent for longer than 2 weeks).
11. History of stroke or intracranial hemorrhage within 2 months before the first dose of study drug.
12. History of bleeding diathesis (e.g., hemophilia or von Willebrand disease).
13. Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before screening.
14. Major surgical procedure within 28 days of first dose of study drug. Note: If a subject had major surgery, they must have recovered adequately from any toxicity and/or complications from the intervention before the first dose of study drug.
15. Requires treatment with a strong CYP3A inhibitor.
16. Requires treatment with proton-pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). Subjects receiving proton-pump inhibitors who switch to H2-receptor antagonists or antacids are eligible for enrollment to this study.
17. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon).
18. Absolute neutrophil count (ANC) $<0.75 \times 10^9$/L or platelet count $<50 \times 10^9$/L, unless there is bone marrow involvement.
19. Total bilirubin >1.5 x upper limit of normal (ULN); or AST or ALT >3.0 x ULN.
20. Estimated CrCL of <30 mL/min, calculated using the formula of Cockcroft and Gault [(140-Age) • Mass (kg)/(72 • creatinine mg/dL) • multiply by 0.85 if female].
21. Breastfeeding or pregnant.
22. Concurrent participation in another therapeutic clinical trial.

3.4.3 Replacement of Subjects

Subjects who are withdrawn or removed from study treatment will not be replaced.

3.4.4 Enrollment Procedures

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

- The study center will notify the sponsor when a clinically eligible subject is identified and is ready to screen, to ensure enrollment availability on the study.
- After the subject has signed and dated the ICF, all screening procedures have been completed, and eligibility has been confirmed, the subject can be officially enrolled into 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 48 hours.

Treatment must begin within the screening window (Section 4.1).

A CT scan documenting progression while off ibrutinib treatment or other objective criteria (e.g., absolute lymphocyte count [ALC] increasing >50%) must be available for review by the sponsor.

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

Acalabrutinib is manufactured according to cGMP regulations and will be provided to the investigational site by Acerta Pharma or designee. Acalabrutinib should be stored according to the instructions on the label affixed to the package of the drug product. Acalabrutinib will be provided in white, high-density polyethylene bottles.

If a drug shipment arrives damaged, or if there are any other drug complaints, a Product Complaint Form should be completed and 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 trial.

3.5.3 Administration of Study Drug

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

Acalabrutinib 100 mg is intended to be administered orally BID with 8 ounces (approximately 240 mL) of water. Doses should be administered 12 hours apart (a window of ±1 hour is allowed). The capsules should be swallowed intact. Subjects should not attempt to open capsules or dissolve them in water.

If a dose is not taken within the allowed window, it can be taken up to 3 hours after the scheduled time with a return to the normal schedule the same or following day. 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.

Guidance on coadministration of acalabrutinib with agents that affect gastric pH is provided in Section 3.10.10.

For subjects considered at risk for TLS, administer appropriate hydration and allopurinol or rasburicase per institutional standards prior to initiating treatment.

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 acalabrutinib treatments will be taken at home. Subjects will receive a drug diary to record the specific time each dose was taken and to record reasons for any missed doses.

Subject compliance with acalabrutinib dosing will be assessed at every visit. The subject will be instructed to bring the diary and any remaining capsules to the clinic at their next visit. The study staff will review the diary and ask the subject if all of the capsules were administered. Any remaining or returned capsules will be counted and recorded as described in Section 7.6. Returned capsules must not be redispensed to another subject.

3.6 STUDY TREATMENT SCHEDULE

Acalabrutinib 100 mg BID will be administered orally.

For information on dosing and dose modifications of acalabrutinib, refer to Section 3.8.

3.7 DURATION OF THERAPY

Treatment can continue until the end of study for subjects without disease progression and who are tolerating therapy. The end of study is defined as the date of the last subject's last visit. Refer to Section 3.11 for details on withdrawal of study treatment.

3.8 DOSING DELAYS AND MODIFICATIONS

3.8.1 Dose Delays and Modifications of Acalabrutinib

Subjects should be followed closely for AEs or laboratory abnormalities that might indicate acalabrutinib–related toxicity. If a subject experiences an intolerable AE during

the course of therapy, then acalabrutinib should be withheld, as necessary, until the AE resolves or stabilizes to an acceptable degree.

The actions in Table 1 should be followed for the following treatment-emergent toxicities:

- Grade 4 ANC (<500/μL) for >7 days (neutrophil growth factors are permitted per American Society of Clinical Oncology [ASCO] guidelines [Smith 2015] and use must be recorded on the 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 Modification 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 one dose level lower (100 mg QD)
4th	Discontinue acalabrutinib

QD=once per day.

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 100 mg BID for this protocol.

Treatment with acalabrutinib should be withheld 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 withheld 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.

For full study treatment discontinuation criteria, refer to Section 3.11.

Note: Temporary withholding of acalabrutinib (e.g., for drug-related toxicity, surgery, or intercurrent illness) for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. In such circumstances, and if medically appropriate, subjects may resume therapy and relevant clinical, laboratory, and/or radiographic assessment can be attempted to document whether tumor control can be maintained or whether cancer progression has occurred**.**

3.9 CONCOMITANT THERAPY

3.9.1 Permitted Concomitant Therapy

Antiemetics are permitted if clinically indicated. Standard supportive care medications are permitted as per institutional standards. Use of hematopoietic growth factors is permitted per the ASCO guidelines (Smith 2015).

3.9.2 Prohibited or Restricted Concomitant Therapy

Any chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy for treating CLL are prohibited if being used to treat the disease initially under study. High-dose corticosteroids used to treat underlying CLL 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.

The concomitant use of strong inhibitors/inducers of CYP3A (see Appendix 4) should be avoided when possible (see Section 3.10.9 and Section 3.10.10). If a subject requires short-term treatment with a strong CYP3A inhibitor (i.e., anti-infectives for up to 7 days), interrupt acalabrutinib treatment.

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

100 mg BID after stopping the strong CYP3A inducer. For additional information on drugs with potential drug-drug interactions, refer to Section 3.10.10.

3.10 RISKS ASSOCIATED WITH ACALABRUTINIB TREATMENT

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

3.10.1 Hemorrhage

Bleeding events, some fatal, including CNS, respiratory, and gastrointestinal hemorrhage, have been reported in subjects treated with acalabrutinib.

Subjects receiving antithrombotic agents may be at increased risk of hemorrhage. Use caution with antithrombotic agents and consider additional monitoring for signs of bleeding when concomitant use is medically necessary. As a precaution, it is suggested that acalabrutinib be withheld for at least 3 days pre- and post-surgery.

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

3.10.2 Infections

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

Consider prophylaxis in subjects who are at increased risk for opportunistic infections. Subjects should be monitored for signs and symptoms of infection and treated as medically appropriate. Refer to Sections 3.10.3 and 4.1.14 for additional information and monitoring guidance for viral hepatitis, and Section 3.10.4 for additional information and management guidance for signs and symptoms of progressive multiofocal leukoencophalopathy (PML).

3.10.3 Hepatitis B Virus Reactivation

Cases of hepatitis B virus (HBV) reactivation have occurred in clinical studies with acalabrutinib. Subjects who are anti-HBc positive, or have a known history of HBV infection, should be monitored every 3 months with a quantitative PCR test for HBV DNA. Monitoring should continue every 3 months 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.

3.10.4 Progressive Multifocal Leukoencephalopathy

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

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

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

If PML is confirmed, permanently discontinue acalabrutinib.

3.10.5 Cytopenias

Grade 3 or 4 events of cytopenias, including neutropenia, anemia, and thrombocytopenia have occurred in clinical studies with acalabrutinib. Monitor blood counts as specified in the schedule of assessments and as medically appropriate. Please refer to Section 3.8 for study drug modification guidance. Subjects with cytopenias should be managed according to institutional guidelines or as clinically indicated.

3.10.6 Second Primary Malignancies

Second primary malignancies, including solid tumors and skin cancers, have been reported in patients treated with acalabrutinib. The most frequent second primary malignancy was skin cancer(basal cell carcinoma). Subjects should be monitored for signs and symptoms of malignancy. Subjects who develop a second primary malignancy should be managed according to institutional guidelines with diagnostic evaluations as clinically indicated, and it may be necessary for subjects to permanently discontinue study treatment. Continuation of acalabrutinib treatment should be discussed with the medical monitor. Please refer to Section 6.2.3 for second primary malignancy reporting guidance.

3.10.7 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, and 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 appropriate.

3.10.8 Reference Safety Information

For the purpose of reporting AEs and SAEs:

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

3.10.9 Dietary Restrictions

Acalabrutinib can be taken with or without food. St John's wort is a potent CYP3A inducer and should be avoided in subjects treated with acalabrutinib, which is partially metabolized by CYP3A.

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

3.10.10 Drug-Drug Interactions

Acalabrutinib is not a strong direct inhibitor or inducer or CYP isoforms; thus, acalabrutinib, at the currently used clinical doses, is unlikely to be a perpetrator of a drug-drug interaction at the level of inhibition or induction of CYP isoforms. Acalabrutinib is partially metabolized by CYP3A; its exposure is affected when coadministered with strong CYP3A inducers or inhibitors. Consequently, the concomitant use of strong inhibitors/inducers of CYP3A (see Appendix 4) should be avoided when possible.

Based on these considerations, subjects who require therapy with drugs listed in Appendix 4 should not be enrolled into the study. If medically justified, subjects may be enrolled if such inhibitors or inducers can be discontinued or alternative drugs that do not affect these enzymes can be substituted within 7 days before first dose of study drug. If a subject requires a strong or moderate CYP3A inhibitor while on study, the subject should be monitored closely for potential toxicities.

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

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

3.10.11 Reproductive Toxicity

Definition of women of non-reproductive potential:

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

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

Definition of contraception:

> Practice abstinence† from heterosexual activity;
>
> OR
>
> Use (or have their partner use) highly effective contraception during heterosexual activity.

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

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

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

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

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

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.

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

Subjects should promptly notify the investigator if they, or their partners, become pregnant during this study, or 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 female partner must be reported as outlined in Section 6.2.4.

3.10.12 Overdose Instructions

For any subject experiencing an acalabrutinib overdose (ingestion of more than the recommended dosage), observation for any symptomatic side effects should be instituted, and vital signs, biochemical and hematologic parameters 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 of acalabrutinib is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered.

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

3.11 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:

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

Subjects who discontinue study therapy will continue to be followed on study for follow-up of safety (Section 4.2), and survival, unless they withdraw consent for further follow-up. Thus, all subjects receiving ≥1 dose of study drug will be followed during the immediate post-therapy and long-term follow-up (LTFU) assessments unless the subject withdraws consent for such follow-up to be conducted (Section 4.3). The date the subject is withdrawn from study treatment or from the study (including LTFU) and the reason for discontinuation will be recorded and also should be described on the appropriate CRF.

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

3.12 REASONS FOR STUDY EXIT

Reasons for study exit include:

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

3.13 DATA AND SAFETY MONITORING

This trial will be monitored in accordance with the sponsor's pharmacovigilance procedures. AEs and SAEs will be reviewed internally as part of ongoing safety surveillance. Quarterly conference calls with the investigators and applicable site staff will be conducted to discuss study progress, obtain investigator feedback and exchange, and discuss "significant safety events" (i.e., AEs leading to dose reductions, related SAEs, and deaths).

In addition, an independent data monitoring committee (DMC) will be formed to review data for subject safety. Data review will be focused on, but not limited to deaths, treatment discontinuations, SAEs, and Grade 3/4 AEs, as well as special events of interest. After review of data, the DMC will provide recommendations regarding stopping or continuing the study in accordance with the DMC charter. The DMC will meet approximately when the first 15 subjects have been treated through Week 8, 30 subjects have been treated through Week 8, and subsequently every year, as needed, until the

final DCO and database closure for the study. Additional meetings may be scheduled at the request of the DMC or the sponsor.

4.0 STUDY ACTIVITIES AND ASSESSMENTS

The schedule of events is provided in Appendix 1. Descriptions of the scheduled evaluations are outlined below and complete information on study drug and dosing is provided in Section 3.5.

Before study entry, throughout the study, and at the follow-up evaluation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. This study will primarily use central laboratory testing for laboratory evaluations. Samples from sites' local laboratories will 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 ICF approved by the IRB/IEC, confirming his or her willingness to participate in this study before initiating any screening activity that is not considered standard of care by institutional standards. Subjects must also grant permission to use protected health information, if required by local regulations.

4.1.2 Medical History

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

4.1.3 Adverse Events

The accepted regulatory definition for an AE is provided in Section 6.1. The AE reporting period is described in Section 6.2.1. Important additional requirements for reporting SAEs are explained in Section 6.2.

4.1.4 Concomitant Medications and Therapy

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

4.1.5 Confirmation of Eligibility

Subject eligibility for enrollment will be assessed per Section 3.4. All screening procedures, unless otherwise indicated, should be completed within 30 days of the first dose of study drug.

4.1.6 ECOG Performance Status

The ECOG performance index is provided in Appendix 5.

4.1.7 Physical Examination, Vital Signs, Height and Weight, and Disease-Related Symptoms

The screening physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and lymphatic system.

Symptom-directed physical examinations, including attention to neurologic signs and symptoms of PML, will be done during the treatment period and at the TT and SFU visits and during the post-treatment disease follow-up.

Disease-related symptoms will be assessed and recorded in the subject records and are defined per Hallek 2008 as:

a. Unintentional weight loss of 10% or more within the previous 6 months;
b. Significant fatigue (i.e., ECOG performance status 2 or worse; inability to work or perform usual activities);
c. Fevers higher than 100.5°F or 38°C for 2 or more weeks without other evidence of infection; or
d. Night sweats for more than 1 month without evidence of infection

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

4.1.8 Electrocardiogram

Subjects should be supine and resting for ≥10 minutes before the baseline electrocardiogram (ECG).

4.1.9 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.

4.1.10 Hematology

Hematology studies must include CBC with differential including, but not limited to white blood cell count, hemoglobin, hematocrit, platelet count, ANC, and ALC. Testing will be done by a local or central laboratory as listed on the investigator's Form FDA 1572.

4.1.11 Serum Chemistry

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

4.1.12 Urinalysis

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

4.1.13 CCI

CCI

4.1.14 Hepatitis B and C Testing

Hepatitis serology testing must include HBsAg, hepatitis B surface antibody (anti-HBs), anti-HBc, and hepatitis C virus (HCV) antibody. In addition, any subjects testing positive for any hepatitis serology must have PCR testing during screening and on study (see Appendix 1 and exclusion criterion #9). Testing will be done by local or central laboratory.

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

Subjects with a known history of hepatitis C or who are hepatitis C antibody positive should be tested for HCV RNA during screening and at Cycle 6. No further testing beyond Cycle 6 is necessary if PCR results are negative.

Refer to Section 3.10.3 and Appendix 1 regarding monitoring of subjects who are anti-HBc positive or hepatitis C antibody positive or who have a known history of HBV or HCV.

4.1.15 Serum Immunoglobulin

Testing for immunoglobulin G (IgG), IgM, IgA, and total immunoglobulin (if available) will be done by a local or central laboratory as listed on the investigator's Form FDA 1572.

4.1.16 CCI

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CCI [redacted]

4.1.17 CCI [redacted]

CCI [redacted]

4.1.18 Bone Marrow Aspirate and Biopsy

For Eligibility

A unilateral bone marrow aspirate and biopsy will be done at screening or ≤3 months before enrollment. Subjects who have a bone marrow aspirate and biopsy results may use these results in lieu of the baseline bone marrow aspirate/biopsy required for this study, provided the biopsy/aspirate was done within 3 months before enrollment.

Response Evaluation

If the subject's physical examination findings, laboratory evaluations, and radiographic evaluations suggest that CR has been achieved in all response parameters, a bone marrow aspirate and biopsy and peripheral blood sample must be obtained to confirm the CR and to evaluate minimal residual disease by flow cytometry. The bone marrow aspirate and biopsy and the peripheral blood sample must be done within 4 weeks of the CT scan that showed CR. In cases where cytopenic progression is suspected, a bone marrow aspirate or biopsy should be performed to distinguish autoimmune and drug-related cytopenias.

4.1.19 CT Scans

Pretreatment radiologic tumor assessment should be performed within 30 days before the first dose. Radiologic tumor assessment will also be performed at the end of Cycles 3, 6, 9, 12, 18, 24 (-7 days), and then every year thereafter, while receiving acalabrutinib treatment. Note: Please refer to Section 3.8.1 regarding the potential for tumor flare during drug holds. Therefore, we recommend not staging subjects (e.g., with CT scans) during drug holds.

Confirmation of CR will require bone marrow analysis and radiologic tumor assessment. Radiological imaging by CT with contrast is required and must include the pelvis, abdomen, chest, and neck (and any other disease area). Subjects who are intolerant to intravenous (IV) CT contrast agents will have CT scans performed with oral contrast. When possible, all subjects should have radiographic tumor measurements done at the participating study center or at 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 as much as possible. MRI may be used to evaluate nontarget 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.

CT scans will be performed until disease progression is confirmed, regardless of whether or not the subject remains on treatment. In the event disease progression is suspected due to physical examination or laboratory test, a CT scan must be performed to confirm disease progression. There must be radiographically measurable disease at screening (≥1 lymph node >1.5 cm in the longest diameter).

A central imaging service will be used to provide independent radiologic assessments for the purposes of the primary endpoint. These measurements will not be reported back to the site.

4.1.20 Routine Clinical Assessments

Routine clinical assessments include physical examinations, recording of symptoms, and hematologic evaluations to evaluate for both AEs and for disease progression at times when the CT scan is not obtained.

4.1.21 Overall Response Evaluations

Overall response assessments will include evaluation of physical examinations, recording of symptoms, hematologic evaluations (Note: CBC with differential must be done within 7 days and bone marrow aspirate/biopsy [when applicable] must be done within 4 weeks of the contemporaneous radiographic evaluation), and radiographic evaluations per the schedule of assessments. Subjects who have signs and symptoms of progression outside of the scheduled assessment should be evaluated by the investigator with a physical examination and a CBC with differential to determine if disease progression is present. The blood samples for response or disease progression determination should be confirmed by a central laboratory (samples from local laboratories can be used if central testing is unavailable). Any suspected case of disease progression should be confirmed with a CT scan if one was not obtained and should be reported to the sponsor or designee. Subjects may continue study treatment until progression is confirmed by a serial examination at least 2 weeks later. In addition, when clinically appropriate, based on investigator perceived risk-benefit assessment, a subject may continue treatment and remain under close observation until progression is confirmed. New anticancer therapy should be withheld if clinically appropriate in the absence of confirmed progressive disease.

4.2 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 of a scheduled study visit.

In addition to the TT 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. 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 1) describes the procedures required for the TT and SFU visits.

4.3 FOLLOW-UP FOR PROGRESSION

4.3.1 Post-Treatment Disease Follow-Up

Each subject should be followed until disease progression. If disease progression has not occurred at the time of the 30-day SFU visit, post-treatment disease follow-up visits should occur approximately every 3 months (12 weeks) until disease progression, regardless of whether the subject receives new anticancer treatment. During this period, subjects will be followed via CT scans, CBC with differential, physical examinations (including vital signs and weight), serum chemistry, and bone marrow biopsy and aspirate (as clinically indicated). Refer to Appendix 1 for the full list of assessments required during this period.

4.3.2 Long-Term Follow-Up

Once subjects progress—for all subjects who have not withdrawn consent—they will be contacted approximately every 3 months (12 weeks) by clinic visit or telephone, to assess survival and the use of alternative anticancer therapy until death or loss to follow-up.

4.4 MISSED EVALUATIONS

Missed evaluations should be rescheduled and performed as close to the original scheduled date as possible. An exception is made when rescheduling becomes, in the investigator's opinion, medically unnecessary or unsafe because it is too close in time to the next scheduled evaluation. In that case, the missed evaluation should be abandoned.

5.0 STATISTICAL METHODS OF ANALYSIS

5.1 GENERAL CONSIDERATIONS

The statistical methods presented in this section provide a high-level summary of analysis to be performed for this study. Detailed analyses will be described in the Statistical Analysis Plan (SAP). The SAP will be finalized before database lock. Any changes to the methods described in the final SAP will be justified and described in the clinical study report.

No interim analysis is planned for this study. The primary analysis will be performed after all subjects have completed the study.

Continuous variables will be summarized by number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by the number of subjects and percentage in each category.

5.2 RATIONALE FOR SAMPLE SIZE

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5.3 ANALYSIS POPULATIONS

The analysis populations for statistical analyses and study summary are defined as follows:

- **All-treated population**: All enrolled subjects who receive ≥1 dose of study drug
- **Efficacy-evaluable (EE) population**: All subjects in the All-treated population who have ≥1 radiologic response assessment after the first dose of study drug.

The All-treated population is the primary analysis population for efficacy and safety summaries. The EE population will be used for sensitivity analyses.

5.4 MISSING DATA HANDLING

Subjects not evaluable for ORR due to a lack of postbaseline response assessment will be counted as a non-responder in the primary analysis using the All-treated population. Alternatively, those non-evaluable subjects will be excluded from the ORR calculation using the EE population for a sensitivity analysis.

5.5 ENDPOINT DATA ANALYSIS

5.5.1 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized using descriptive statistics. Demographic summaries will include age, sex, race and/or ethnicity. Baseline characteristics will include disease-related parameters of interest before dosing.

5.5.2 Study Treatment Administration and Compliance

Descriptive statistics will be provided to summarize study treatment administration and compliance. The total number of doses taken, the number of days of treatment, the number of missing doses, and relative dose intensity will be presented.

5.5.3 Analysis of Efficacy Endpoints

5.5.3.1 Primary Efficacy Endpoint

Overall Response Rate (ORR)

ORR is defined as the proportion of subjects achieving a best overall response (BOR) of either CR, complete remission with incomplete bone marrow recovery (CRi), nodular partial remission (nPR), or PR at or before initiation of subsequent anticancer therapy. ORR will be analyzed per investigator's assessment.

ORR and the associated 95% exact (Clopper-Pearson) CI will be provided. ORR will also be tested against the historical control of 21%, as assumed for the sample size calculation, using the exact binomial test.

5.5.3.1 Secondary Efficacy Endpoints

Duration of Response (DOR)

DOR is defined as the duration from time of initial response until documented disease progression. Initial response includes CR, CRi, nPR, or PR.

Progression-Free Survival (PFS)

PFS is defined as the time from date of first dose to date of first documented disease progression by investigator or death due to any cause, whichever comes first.

Time-to-Next Treatment (TTNT)

TTNT is defined as the time from date of first dose to date of institution of subsequent anticancer therapy for CLL or death due to any cause, whichever comes first. Subjects who do not start anticancer therapy or die before the data cutoff date will be censored at the date of last visit.

Overall Survival (OS)

OS is defined as the time from date of first dose to date of death due to any cause.

Kaplan-Meier (K-M) methods will be used to estimate the distribution of DOR, PFS, TTNT, and OS. K-M point estimates and corresponding 95% CIs will be calculated at 25^{th} percentile, median (50^{th} percentile), 75^{th} percentile, and selected landmark points.

5.5.4 Safety Endpoint

All reported AEs will be mapped to MedDRA. Prior and concomitant medications will be recorded and coded using World Health Organization Drug Dictionary (WHODRUG).

The frequency (number and percentage) of treatment-emergent AEs will be tabulated by system organ class (SOC) and preferred term (PT). Summaries will also be presented by the severity of the AE and by relationship to study drug. Laboratory shift tables containing numbers and percentages will be presented by laboratory parameter. Figures of changes in laboratory parameters over time will be generated. Prior and concomitant medications will be summarized by anatomical therapeutic chemical (ATC)

classification system and preferred term. Vital signs and other safety endpoints may be tabulated as needed.

5.5.5 CCI

CCI [redacted]

6.0 ASSESSMENT OF SAFETY

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

6.1 DEFINITIONS

6.1.1 Adverse Events

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

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with CLL 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 enrollment in the study will not be considered serious if they are performed after enrollment in the study 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 (e.g., a blood transfusion for low hemoglobin) or requires a change in study drug (e.g., lowering the dose or withholding study drug while the laboratory finding resolves or stabilizes).
- Progression of underlying malignancy: Progression of underlying malignancy will not be reported as an AE if it is clearly consistent with the suspected progression of the underlying cancer. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as an SAE. Clinical symptoms of

progression may be reported as AEs if the symptoms cannot be determined as exclusively due to the progression of the underlying malignancy, or if they do not fit the expected pattern of progression for the disease under study.

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

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

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 inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent 1 of the outcomes listed above).

6.1.3 Severity

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

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

6.1.4 Adverse Events of Special Interest

The following events are adverse events of special interest (AESIs) and must be reported to the sponsors 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)

6.2 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 must be reported on the SAE form or clinical database.

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 will be reported until 30 days after the last dose of study drug(s) or the start of new anticancer therapy (whichever comes first). After this period, investigators should report SAEs or other AEs of concern that 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 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, or detected through physical examination, or other means, will be recorded in the subject's medical record and on the AE CRF.

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

See Appendix 6 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 fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as nonserious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumor event in question is a new malignant tumor (i.e., it is not the tumor for which entry into the study is a criterion and that is being treated by the investigational product (IP) under study and is not the development of new or progression of existing metastasis to the tumor under study). Malignant tumors that—as part of normal, if rare, progression—undergo transformation (e.g., Richter's transformation of B-cell chronic lymphocytic leukemia into diffuse large B-cell lymphoma) should not be considered a new malignant tumor.

6.2.4 Pregnancy

The investigator should report all pregnancies and pregnancies in the partners of subjects within 24 hours using the Pregnancy Report Form. This form should be faxed or emailed to Acerta Pharma Drug Safety. Any pregnancy-associated SAE must be reported to Acerta Pharma, according to the usual timelines and directions for SAE reporting (Section 6.2.5).

Any uncomplicated pregnancy that occurs with the subject or with the partner of a treated subject during this study will be reported. All pregnancies and partner pregnancies that are identified during or after this study, wherein the estimated date of conception is determined to have occurred from the time of consent to 2 days after the last dose of acalabrutinib will be reported, followed to conclusion, and the outcome reported, as long as the subject or partner has consented to participate in follow-up.

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

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

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

6.2.5 Expedited Reporting Requirements for Serious Adverse Events

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

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

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

An SAE may qualify for mandatory expedited reporting to regulatory authorities if the SAE is attributable to the investigational product (or if a causality assessment is not provided for the SAE, in which case a default of ‘related’ may be used for expedited reporting purposes) and the SAE is not listed in the current Acalabrutinib Investigator Brochure (i.e., an unexpected event). In this case, Acerta Pharma Drug Safety/Designee will forward a formal notification describing the suspected unexpected

serious adverse reaction (SUSAR) to all investigators. Each investigator must then notify his or her IRB/IEC of the SUSAR.

Drug Safety Contact Information	
Fax:	PPD (United States) (for outside the United States)
Email:	PPD

6.2.6 Type and Duration of Follow-up of Subjects after Adverse Events

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

6.2.7 Hy's Law

Cases where a subject shows elevations in liver biochemistry may require further evaluation, and occurrences of AST or ALT ≥3×ULN together with total bilirubin ≥2×ULN may need to be reported as SAEs. Please refer to Appendix 7 for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

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 are:

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

7.1 INSTITUTIONAL REVIEW BOARD AND INDEPENDENT ETHICS COMMITTEE

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

7.2 INFORMED CONSENT AND PROTECTED SUBJECT HEALTH INFORMATION AUTHORIZATION

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

In accordance to 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.

7.3 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.

7.4 CASE REPORT FORMS

Authorized study site personnel (see Section 7.11) will complete CRFs designed for this study according to the completion guidelines that will be provided within the clinical database. The investigator will ensure that the CRFs are accurate, complete, legible, and completed promptly. Refer to Section 7.7 for record retention requirements.

7.5 STUDY MONITORING REQUIREMENTS

Representatives of Acerta Pharma or its designee will monitor this study until completion. The purpose of monitoring is to ensure compliance with the protocol and the quality and integrity of the data. This study is also subject to reviews or audits.

Every effort will be made to maintain the anonymity and confidentiality of all subjects during this clinical study. However, because of the experimental nature of this treatment, the investigator agrees to allow the IRB/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.

7.6 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 the protocol.

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

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

7.7 RECORD RETENTION

The investigator and other appropriate study staff are responsible for maintaining all documentation relevant to the study. Mandatory documentation includes copies of study protocols and amendments, each Form FDA 1572, IRB/IEC approval letters, signed ICFs, drug accountability records, SAE information transmitted to Acerta Pharma, subject files (source documentation) that substantiate entries in CRFs, all relevant correspondence and other documents pertaining to the conduct of the study.

An investigator shall retain records for a period of at least 2 years after the date the last marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. The investigator must notify Acerta Pharma and obtain written approval from Acerta Pharma before destroying any clinical study records at any time. Acerta Pharma will inform the investigator of the date that study records may be destroyed or returned to Acerta Pharma.

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

7.8 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 trial.

7.9 PUBLICATION OF STUDY RESULTS

Authorship, in general, will follow the recommendations of the (ICMJE 2014).

7.10 CLINICAL TRIAL INSURANCE

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

7.11 GENERAL INVESTIGATOR RESPONSIBILITIES

The principal investigator must ensure that:

1. He or she will conduct or supervise the study.
2. His or her staff and all persons who assist in the conduct of the study clearly understand their responsibilities and have their names included in the Study Personnel Responsibility/Signature Log.
3. The study is conducted according to the protocol and all applicable regulations.
4. The protection of each subject's rights and welfare is maintained.
5. Signed and dated informed consent and, when applicable, permission to use protected health information are obtained from each subject before conducting 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 (IND) Safety Reports/ SUSAR Reports are submitted promptly to the IRB/IEC.
12. All SAEs are reported to Acerta Pharma Drug Safety/Designee within 24 hours of knowledge via the clinical database and to the IRB/IEC per their requirements.

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Appendix 1 Schedule of Assessments

		Treatment Phase[a]														
	Screening[b]	**Cycle 1**			**Cycle 2**		**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**Cycles 9, 15, 21, 27, ≥33**	**Cycles 12, 18, 24, 30, ≥36**	**Response Evaluation**	**TT Visit[c]**	**SFU Visit[c]**	**Post-treatment Disease Follow-up[d]**	**LTFU[e]**
Days		1	15	28	15	28	28	28	28	28	28	28		+ 7 days after last dose	30 days after last dose	Q12W	Q12W
Study Windows	-30 days		± 2 days		± 2 days		± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days			+ 7 days	± 7 days	± 7 days
Informed consent	x																
Confirm eligibility	x																
Medical history	x																
PE[f]/Vital signs[g]/Weight	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	
Disease-related symptoms	x						x			x	Cycle 9	Cycles 12, 18 & 24	x			x	
ECOG status	x	x	x	x	x	x	x	x	x	x	x	x		x	x		
ECG[h]	x																
Lab assessments:																	
Urine or serum pregnancy test[i]	x	x[j]		x		x	x	x	x	x	x	x		x	x		
Hematology[k]	x		x	x	x	x	x	x	x	x	x	x	ANC, ALC, PLT, Hgb (within 7 days of CT)	x	x	x	
Serum chemistry[l]	x		x	x	x	x	x	x	x	x	x	x		x	x	x	
Urinalysis[m]	x																
CCI																	
Serum Ig[p]		x[o]		x			x			x		Cycle 12, then every 6 cycles				Q24W	

		Treatment Phase[a]														
	Screening[b]	**Cycle 1**			**Cycle 2**		**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**Cycles 9, 15, 21, 27, ≥33**	**Cycles 12, 18, 24, 30, ≥36**	**Response Evaluation**	**TT Visit[c]**	**SFU Visit[c]**	**Post-treatment Disease Follow-up[d]**	**LTFU[e]**
Days		1	15	28	15	28	28	28	28	28	28	28		+ 7 days after last dose	30 days after last dose	Q12W	Q12W
Study Windows	-30 days		± 2 days		± 2 days		± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days			+ 7 days	± 7 days	± 7 days
Hepatitis serology[q]	x																
HBV PCR[r]	x						x			x	Q3M	Q3M				Q3M	Q3M
HCV PCR[s]	x									x							
CCI																	
Bone marrow (aspirate/biopsy)[v]	x											To confirm CR	To confirm CR			As clinically indicated	
CCI																	
Acalabrutinib 100 mg BID		Continuous twice daily dosing															
Study drug compliance		x	x	x	x	x	x	x	x	x	x	x					
CT scans[x]	x[y]						x[z]			x[z]	Cycle 9[z]	Cycles 12, 18 & 24[z]	x[z]			x	
Overall response assessment							x			x	Cycle 9	Cycles 12, 18 & 24	x				
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	
Survival																	x

AE=adverse event; ALC=absolute lymphocyte count; ANC=absolute neutrophil count; anti-HBc=hepatitis B core antibody; anti-HBs anti-HBs=hepatitis B surface antibody; BID=twice daily; CCI BUN=blood urea nitrogen; CLL=chronic lymphocytic leukemia; CR=complete response; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; CCI Hgb=hemoglobin level; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; Ig=immunoglobulin; CCI IV=intravenous; IVIG=intravenous immunoglobulins;

LDH=lactate dehydrogenase; LTFU=long-term follow-up; CCI PE=physical examination; PCR=polymerase chain reaction; CCI
PLT=platelet count; PML=progressive multifocal leukoencephalopathyQ24W=every 24 weeks; Q3M=every 3 months; SFU=safety follow-up; TT=treatment termination.

Footnotes for ACE-CL-208 Schedule of Study Activities:

a. Subjects will have visits every 2 weeks for the first 2 cycles, then monthly through end of Cycle 6, then every 3 cycles thereafter. The end of study is defined as the date of the last subject's last visit. Subjects who are still on treatment at the end of Cycle 36 and deriving clinical benefit from acalabrutinib treatment may continue treatment.
b. Screening tests should be completed within 30 days before the first administration of study drug, unless otherwise indicated.
c. A TT visit is required for subjects who permanently discontinue study drug for any reason (except for death, loss to follow-up, or withdrawal of consent), 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 of a scheduled study visit. In addition to the TT 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. Each subject should be followed until disease progression. If disease progression has not occurred at the time of the 30-day SFU visit, post-treatment disease follow-up visits should occur approximately every 3 months (12 weeks) until disease progression, regardless of whether the subject receives new anticancer treatment. During this period, subjects will be followed via CT scans, CBC with differential, physical examinations (including vital signs and weight), serum chemistry, and bone marrow biopsy and aspirate (as clinically indicated).
e. Once subjects progress—for all subjects who have not withdrawn consent—they will be contacted approximately every 3 months (12 weeks) 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 neurological examinations for signs and symptoms of PML, will be done during the treatment period and at the TT and SFU visits and during the post-treatment disease follow-up.
g. Vital signs (blood pressure, heart rate, and body temperature) will be assessed after the subject has rested in the sitting position.
h. Subjects should be in supine position and resting for ≥10 minutes before the baseline ECG.
i. 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.
j. This urine or serum pregnancy test is to be performed on Cycle 1 Day 1 (-3 days).
k. Hematology must include CBC with differential including but not limited to white blood cell count, hemoglobin, hematocrit, platelet count, ANC, and ALC.
l. Serum chemistry: albumin, alkaline phosphatase, ALT, AST, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid. If an unscheduled ECG is done at any time, then an electrolyte panel (i.e., calcium, magnesium, and potassium) must be done to coincide with the ECG testing.
m. Urinalysis: pH, ketones, specific gravity, bilirubin, protein, blood, and glucose.
n. CCI
o. Samples at the indicated timepoints are to be collected predose.
p. Serum immunoglobulin: IgG, IgM, IgA, and total immunoglobulin (if available). Testing will be performed on Cycle 1 Days 1 and 28, end of Cycles 3, 6, 12, then every 6 cycles therafter.
q. Hepatitis serology must include HBsAg, anti-HBs, anti-HBc, and HCV antibody. In addition, any subjects testing positive for any hepatitis serology, must have PCR testing (see exclusion criterion #9).
r. Subjects who are anti-HBc positive (or have a known history of HBV infection) should have a quantitative PCR test for HBV DNA performed during screening and every 3 months thereafter. Monitoring every 3 months should continue until 12 months after last dose of acalabrutinib. Any subject with a rising viral load (above lower limit of detection) should discontinue acalabrutinib and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B. As IVIG may cause false positive hepatitis serology, monthly PCR testing is not required in subjects who are currently receiving or received prophylactic IVIG within 3 months before

study enrollment and have a documented negative anti-HBc test before the initiation of IVIG therapy. PCR testing should be performed when clinically indicated (e.g., in the setting of rising transaminase levels).

s. Subjects with a known history of hepatitis C or who are hepatitis C antibody positive should be tested for HCV RNA during screening and at Cycle 6. No further testing beyond Cycle 6 is necessary if PCR results are negative.

t. CCI [redacted]

u. CCI [redacted]

v. A bone marrow aspirate and biopsy will be done at screening or ≤3 months before enrollment, and to confirm CR.

w. CCI [redacted]

x. Radiological imaging by CT with contrast is required and must include the pelvis, abdomen, chest, and neck (and any other disease area). Subjects who are intolerant to IV CT contrast agents will have CT scans performed with oral contrast.

y. Pretreatment radiologic tumor assessment should be performed within 30 days before the first dose.

z. Radiologic tumor assessments will be performed at the end of Cycles 3, 6, 9, 12, 18, 24, (-7 days) and then every year thereafter, while receiving acalabrutinib treatment. Otherwise, radiologic tumor assessments are done at investigator discretion. Bone marrow and radiologic assessments are both required for confirmation of a CR. Testing for minimal residual disease will be done on subjects with confirmed CRs. Clinical sites will be used to collect and store CT scan images.

Appendix 2 IWCLL Response Assessment Criteria (Modified from Hallek 2008)

Response	Lymphocytes	Bone Marrow	Physical Examination[a] (Nodes, Liver, Spleen)	Peripheral Blood
CR*	Lymphocytes <4 x 10^9/L	Normocellular <30% lymphocytes No B-lymphoid nodules	Normal (e.g., no lymph nodes >1.5 cm)	ANC >1.5 x 10^9/L[b] Platelets >100 x 10^9/L[b] Hemoglobin >11.0 g/dL (untransfused)[b]
CRi	Lymphocytes <4 x 10^9/L	Hypocellular <30% lymphocytes	Normal (e.g., no lymph nodes >1.5 cm)	Persistent anemia, thrombocytopenia, or neutropenia related to drug toxicity
nPR	CR with the presence of lymphoid nodules in the bone marrow which reflect residual disease.			
PR*	Lymphocytes <5 x 10^9/L Or ≥50% decrease from baseline	Not assessed	≥50% reduction in lymphadenopathy[c] and/or in spleen or liver enlargement	ANC >1.5 x 10^9/L Or Platelets >100 x 10^9/L or 50% improvement over baseline[b] Or Hemoglobin >11.0 g/dL or 50% improvement over baseline (untransfused)[b]
PRL*	Lymphocytes ≥5 x 10^9/L	Not assessed	≥50% reduction in lymphadenopathy[c] and/or in spleen or liver enlargement	ANC >1.5 x 10^9/L Or Platelets >100 x 10^9/L or 50% improvement over baseline[b] Or Hemoglobin >11.0 g/dL or 50% improvement over baseline (untransfused)[b]

Response	Lymphocytes	Bone Marrow	Physical Examination[a] (Nodes, Liver, Spleen)	Peripheral Blood
SD	Absence of PD and failure to achieve at least a PR			
PD*	Lymphocytes ≥50% increase over baseline, with ≥5000 B lymphocytes/µL	Not assessed (except to confirm PD as assessed by progressive cytopenias)	Appearance of any new lesion or de novo appearance of hepatomegaly or splenomegaly Or Increase ≥50% in lymphadenopathy Or Increase ≥50% in hepatomegaly Or Increase ≥50% in splenomegaly	Platelets decrease of ≥50% from baseline secondary to CLL Or Hemoglobin decrease of >2 g/dL from baseline secondary to CLL

ANC=absolute neutrophil count; CLL=chronic lymphocytic leukemia; CR=complete remission (response); CRi=CR with incomplete bone marrow recovery; CT=computed tomography; IWCLL=International Workshop on Chronic Lymphocytic Leukemia; nPR=nodular partial remission; PD=progressive disease; PR=partial remission (response); PRL=partial remission (response) with lymphocytosis; SD=stable disease.

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

a CT scan of abdomen, pelvis, and thorax may be used if previously abnormal.

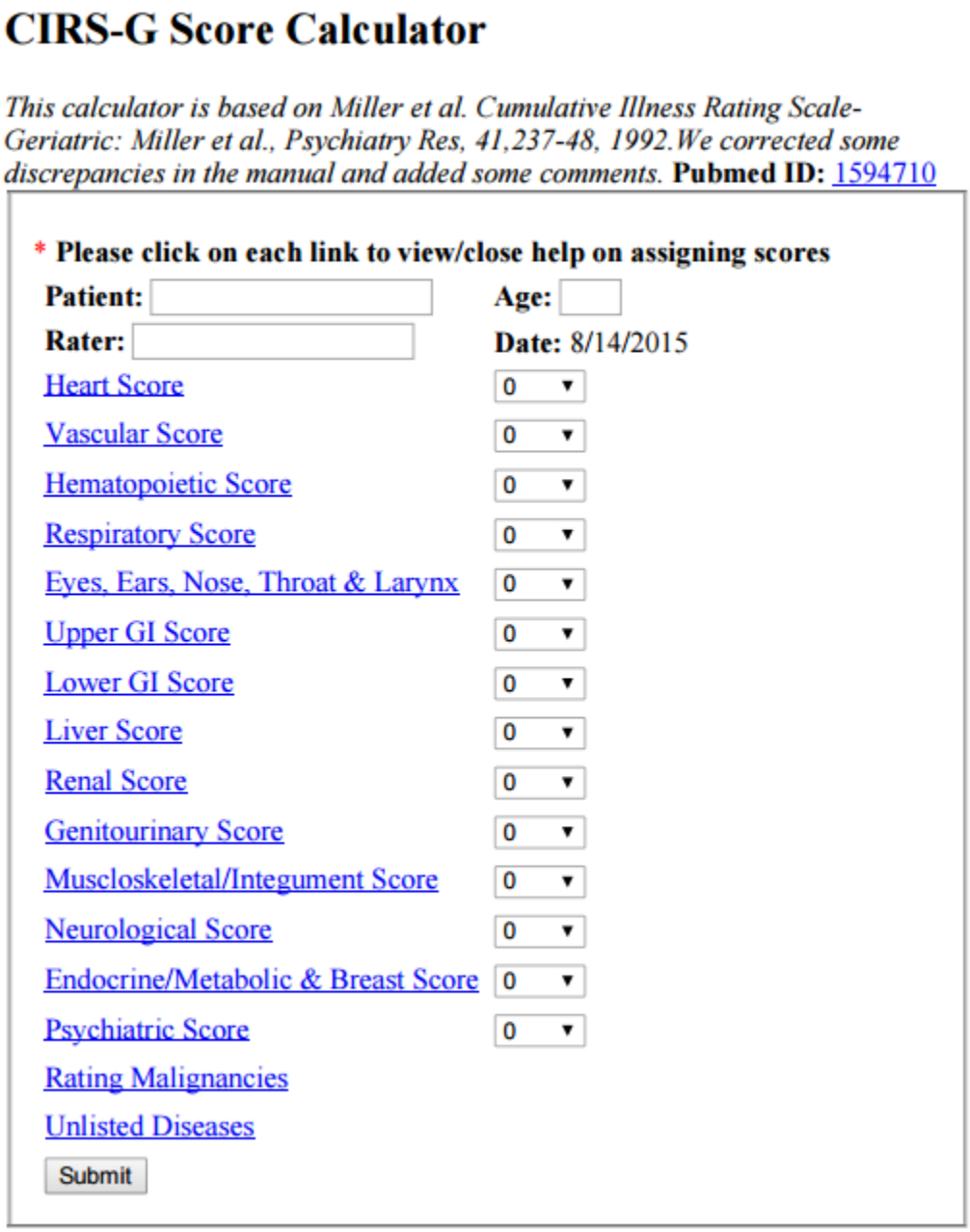
b Without need for exogenous growth factors.

c In the sum products of ≤6 lymph nodes or in the largest diameter of the enlarged lymph node(s) detected before therapy and no increase in any lymph node or new enlarged lymph nodes.

Appendix 3 Cumulative Illness Rating Scale-Geriatric (CIRS-G) Calculator

Web-based CIRS-G calculator link:

http://eforms.moffitt.org/cirsgScore.aspx



CIRS-G Score Calculator

This calculator is based on Miller et al. Cumulative Illness Rating Scale-Geriatric: Miller et al., Psychiatry Res, 41,237-48, 1992.We corrected some discrepancies in the manual and added some comments. **Pubmed ID:** 1594710

* **Please click on each link to view/close help on assigning scores**

Patient: **Age:**

Rater: **Date:** 8/14/2015

Heart Score	0
Vascular Score	0
Hematopoietic Score	0
Respiratory Score	0
Eyes, Ears, Nose, Throat & Larynx	0
Upper GI Score	0
Lower GI Score	0
Liver Score	0
Renal Score	0
Genitourinary Score	0
Muscloskeletal/Integument Score	0
Neurological Score	0
Endocrine/Metabolic & Breast Score	0
Psychiatric Score	0
Rating Malignancies	
Unlisted Diseases	

Submit

Appendix 4 Known Strong in Vivo Inhibitors or 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	

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.

a. A strong inhibitor for CYP3A is defined as an inhibitor that increases the area under the concentration-time curve (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.

Source: FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Web link Accessed 11 June 2015: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#inVivo.

Appendix 5 Performance Status Scores

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

As published in Am J Clin Oncol:

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

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

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

Appendix 6 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 7 Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

INTRODUCTION

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

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

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

DEFINITIONS

Potential Hy's Law

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

Hy's Law

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

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

IDENTIFICATION OF POTENTIAL HY'S LAW CASES

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

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

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

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

REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

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

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

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

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

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

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

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

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

ACTIONS REQUIRED FOR REPEAT EPISODES OF POTENTIAL HY'S LAW

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

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

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

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

- If the answer is **No:**

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

- If the answer is **Yes**:

  > Determine whether there has been a significant change in the subject's condition compared with the previous occurrence of PHL. Note: A "significant" change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator; this may be in consultation with the study medical monitor if there is any uncertainty.
  >
  > - If there is no significant change, no action is required.
  > - If there is a significant change, follow the process described in "Potential Hy's Law Criteria Met" in this Appendix for reporting PHL as an SAE.

LABORATORY TESTS

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

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

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

Reference

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