PROTOCOL

TITLE:	A Randomized, Multicenter, Open-Label, Non-Inferiority, Phase 3 Study of ACP-196 Versus Ibrutinib in Previously Treated Subjects with High Risk Chronic Lymphocytic Leukemia
PROTOCOL NUMBER:	ACE-CL-006
STUDY DRUG:	ACP-196 (acalabrutinib)
IND NUMBER:	118717
EUDRACT NUMBER:	2014-005530-64
SPONSOR MEDICAL MONITOR:	PPD Acerta Pharma, BV Phone PPD Email:
SPONSOR:	Acerta Pharma BV PPD 5349 AB Oss The Netherlands
Original Protocol Date:	Version 0.0 – 02 March 2015
Amendment 1 Date:	Version 1.0 – 25 March 2015
Amendment 2 Date:	Version 2.0 – 01 April 2015
Amendment 3 Date:	Version 3.0 – 01 March 2016
Amendment 4 Date:	Version 4.0 – 14 December 2017
Amendment 5 Date:	Version 5.0 – 21 October 2020

Confidentiality Statement

PROTOCOL APPROVAL*: AMENDMENT 5*

I have carefully read Protocol ACE-CL-006 entitled "A Randomized, Multicenter, Open-Label, Non-Inferiority, Phase 3 Study of ACP-196 Versus Ibrutinib in Previously Treated Subjects with High Risk Chronic Lymphocytic Leukemia". I agree to conduct this study as outlined herein and in compliance with Good Clinical Practices (GCP), all applicable regulatory requirements, and with the ethical principles laid down in the Declaration of Helsinki. Furthermore, I understand that the Sponsor, Acerta Pharma, and the 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 BV requires that any presentation or publication of study data by clinical investigators be reviewed by Acerta Pharma, before release, as specified in the protocol.

Principal Investigator's Signature Date

Print Name

SUMMARY OF AMENDMENT 5

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

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

Change	Rationale
Global Update: Section numbers added as applicable.	Added additional section numbers to enable ease of locating information in the protocol amendment.
Title Page Updated Medical Monitor.	Updated Medical Monitor and contact information.
Protocol Approval Page Deleted company signatory	Align with other acalabrutinib protocols.
Synopsis Updated to reflect changes in the protocol.	Updated to align with changes in the protocol.
Section 1.2.1 Chemistry Updated approval language to include chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL).	Updated to reflect current CALQUENCE® approval language.
Section 1.3.2 Clinical Experience of Acalabrutinib in CLL Deleted number of participants in clinical studies.	Updated to remove date and number of participants and only reference acalabrutinib Investigator Brochure for latest information.
Section 3.2.3 Exploratory Objectives CCI	CCI
Section 4 Study Design Added rollover language.	Added clarification.
Section 6.1.2 IMBRUVICA (Ibrutinib) Added tablet form of ibrutinib 140-mg.	Updated to reflect availability of capsules and tablets.
Section 6.2.1 Acalabrutinib Removed statement to avoid grapefruit juice and Seville orange juice.	Updated to align with current acalabrutinib Investigator Brochure (version 9.0).
Section 6.2.5.1 Reference Safety Information Added Reference Safety Information section with reference to the Investigator Brochure.	Updated to align with current acalabrutinib Investigator Brochure (version 9.0).
Section 6.2.5.2 Hemorrhage Updated information regarding hemorrhage.	Updated to align with the current acalabrutinib Investigator Brochure (version 9.0).
Section 6.2.5.3 Infections Updated information regarding infections.	Updated to align with current acalabrutinib Investigator Brochure (version 9.0).

Change	Rationale
Section 6.2.5.3.1 Hepatitis B Virus Reactivation Updated information regarding Hepatitis B virus reactivation and monitoring requirements.	Updated to align with current acalabrutinib Investigator Brochure (version 9.0) and to give more detailed guidance on required timing of testing based on the NCCN guidelines.
Section 6.2.5.3.2 Progressive Multifocal Leukoencephalopathy Updated language regarding progressive multifocal leukoencephalopathy.	Updated to align with current acalabrutinib Investigator Brochure (version 9.0).
Section 6.2.5.5 Second Primary Malignancies Updated information regarding second primary malignancies.	Updated to align with current acalabrutinib Investigator Brochure (version 9.0).
Section 6.2.5.6 Atrial Fibrillation Updated information regarding atrial fibrillation.	Updated to align with the current acalabrutinib Investigator Brochure (version 9.0).
Section 6.2.7 Dosage Regimen and Administration for Ibrutinib Added ibrutinib 140-mg tablet.	Updated to reflect availability of ibrutinib capsules and tablets.
Section 6.2.10.2.1 Hepatitis B Virus Reactivation Added hepatitis B virus reactivation language.	Add to reflect current ibrutinib package insert.
Section 6.2.10.8 Cerebrovascular Accidents Added information regarding cerebrovascular accidents and ibrutinib.	Added risk section for cerebrovascular accidents to reflect current ibrutinib package insert.
Section 6.2.10.9 Interstitial Lung Disease Added information regarding interstitial lung disease and ibrutinib.	Added risk section on interstitial lung disease to reflect current ibrutinib package insert.
Section 6.2.10.10 Leukostasis Added information on leukostasis and ibrutinib.	Added risk section on leukostasis to reflect current ibrutinib package insert.
Section 6.2.11 Reproductive Toxicity Updated contraception language.	Updated contraceptive language to reflect acalabrutinib Investigator Brochure (version 9.0). The male contraceptive and sperm donation change was not made in the inclusion criteria because the study is no longer enrolling.
Section 6.3.1 Allowed Concomitant Medications Added information regarding tumor lysis syndrome.	Updated to address health authority feedback.
Section 6.3.2 Guideline for Use of CYP Inhibiting/Inducing Drugs Updated guidance for acalabrutinib.	Updated to reflect current acalabrutinib Investigator Brochure (version 9.0) and the USPI.
Section 6.3.4 Prohibited Concomitant Medications Updated guidance for acalabrutinib.	Updated to align with acalabrutinib Investigator Brochure (version 9.0) and the USPI.

Change	Rationale
Section 6.5 Dietary Restrictions Removed information regarding grapefruit, grapefruit juice and Seville orange juice.	Updated to align with current acalabrutinib Investigator Brochure (version 9.0) and the USPI.
Section 7 Efficacy and Safety Procedures Added reference to Appendix K for management of study procedures during the pandemic.	Added reference to new appendix.
Section 7.1 Description of Procedures Added reference to Schedule of Assessments (Appendix A) to clarify frequency of CT scans.	Added reference to Appendix A, Schedule of Assessments, for frequency of CT scans.
Section 7.1 Description of Procedures Updated information regarding reporting of adverse events.	Updated per Safety recommendation to align with other acalabrutinib protocols.
Section 7.2.2.1 Adverse Event Reporting Period Updated language for AE reporting period.	Updated per Safety recommendation to reflect current language in other acalabrutinib protocols.
Section 7.2.2.3 Adverse Events of Special Interest Added section for adverse events of special interest to include ventricular arrhythmias.	Added section to align with current acalabrutinib Investigator Brochure (version 9.0).
Section 7.2.2.4 Second Primary Malignancies Added section for second primary malignancies.	Added section on second primary malignancies to align with current acalabrutinib Investigator Brochure (version 9.0).
Section 7.2.2.5 Pregnancy Updated contact information to reflect AstraZeneca Representative.	Updated contact information to remove Acerta as process transitions to AstraZeneca.
Section 7.2.2.6 Overdose Instructions Updated language regarding overdose.	Updated to align with acalabrutinib Investigator Brochure (version 9.0) and to include ibrutinib.
Section 7.2.2.7 Expedited Reporting Requirements for Serious Adverse Events/Adverse Events of Special Interest Clarified language to include adverse events of special interest (AESIs). Updated information to reflect AstraZeneca Representative.	Updated per Safety to add AESI reporting language. Updated contact information to remove Acerta as process transitions to AstraZeneca.
Events of Special Interest Deleted section on Events of Special Interest (7.2.2)	Removed to align protocol.
Section 7.2.2.9 Hy's Law Added information regarding Hy's law**.**	Added section on Hy's law to align with other acalabrutinib protocols and AstraZeneca procedure.
Section 8.2 Reasons for Study Exit Updated language regarding study withdrawal.	Updated to provide clarification.
Section 9.6.1 Primary Endpoint and Methods Clarified events and added reference to SAP.	To clarify the primary endpoint PFS is based on IRC assessment. Add

Change	Rationale
	language to allow for ad hoc sensitivity and subgroup analysis.
Section 9.6.2 Secondary Endpoints and Methods Updated SAP statement for clarification.	Updated to provide clarification (editorial change).
Section 9.6.3 Exploratory Endpoints CCI [redacted]	[redacted]
Section 9.7 Safety Analysis Deleted AEs of special interest and other AEs of interest sections for ibrutinib. Updated lymphocytosis section. Updated ECOG performance status and vital signs and weight.	Updated for clarification.
Section 10.9 INVESTIGATOR RESPONSIBILITIES Updated information to reflect AstraZeneca Representative.	Updated contact information to remove Acerta as process transitions to AstraZeneca.
Appendix A: Schedule of Assessments Updated to reflect changes in the protocol.	Aligned with changes made in the protocol.
Appendix C: Examples of Coadministered Drugs That Need Additional Consideration Updated current table and added additional tables regarding coadministration.	Updated with current information from the FDA.
Appendix E: Ibrutinib Full Prescribing and Reference Safety Information Removed this appendix from the protocol amendment.	Removed ibrutinib United States label from the appendix and referenced current label in the protocol.
Appendix J: Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's law Added appendix on Hy's law.	Added appendix on Hy's law to provide additional information to new section added to protocol.
Appendix K: Management of Study Procedures During Pandemic Added appendix to discuss management of study procedures during COVID pandemic.	Added appendix on management of study procedures during the COVID pandemic.

SYNOPSIS

Study Title:	A Randomized, Multicenter, Open-Label, Non-Inferiority, Phase 3 Study of ACP-196 Versus Ibrutinib in Previously Treated Subjects with High Risk Chronic Lymphocytic Leukemia
Protocol Number:	ACE-CL-006
Study Phase:	3
Study Duration:	Approximately *6* years including enrollment time
Investigational Product and Reference Therapy:	The investigational product, ACP-196 (acalabrutinib), will be supplied as hard gelatin capsules for oral administration. Commercially available ibrutinib (IMBRUVICA®) will be used as the reference therapy.
Objectives:	**Primary Objective:** To assess whether acalabrutinib is non-inferior to ibrutinib with respect to progression-free survival (PFS) based on independent review committee (IRC) assessment in subjects with relapsed or refractory chronic lymphocytic leukemia (CLL) with high-risk prognostic markers. The IRC will use the International Workshop on Chronic Lymphocytic Leukemia Criteria (IWCLL; Hallek 2008) with incorporation of the clarification for treatment-related lymphocytosis (Cheson 2012)—hereafter referred to as IWCLL 2008 criteria. **Secondary Objectives**: To evaluate the benefit/risk of acalabrutinib versus ibrutinib in terms of: • Grade ≥ 3 infections • Richter's transformation • Atrial fibrillation • Overall survival (OS) **Safety Objective:** • Safety and tolerability including adverse events (AEs) of interest and laboratory assessments **Exploratory Objectives:** CCI [redacted]

	CCI [redacted]
Study Design:	This randomized, multicenter, open-label, non-inferiority (NI) Phase 3 study is designed to evaluate the efficacy and safety of acalabrutinib (100 mg twice daily) versus ibrutinib (420 mg once daily) in subjects with relapsed or refractory CLL who have high-risk prognostic factors per National Comprehensive Cancer Network guidelines (NCCN Version 1.2016). These high-risk prognostic factors are as follows: • Presence of 17p deletion mutation (17p del) • Presence of 11q deletion mutation (11q del) Approximately 500 eligible subjects will be randomized in a 1:1 ratio into 2 arms to receive either acalabrutinib (Arm A; N=250) or ibrutinib (Arm B; N=250). This study will use an Interactive Web Response System (IWRS) for randomization. Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced, and to enhance the validity of statistical comparisons across treatment groups. Randomization will be performed stratified by the following factors: • Presence of 17p del • Eastern Cooperative Oncology Group (ECOG) performance status (ECOG = 2 versus ECOG ≤1) • Number of prior therapies (1-3 versus ≥ 4) Subject participation will include a Screening Phase, a Treatment Phase, Post-treatment Phase and a Post-disease Progression Phase. The Screening Phase will last up to 28 days before first dose of study drug, during which the subject's eligibility and baseline characteristics will be determined. Treatment with study drug may be continued until an unacceptable drug-related toxicity occurs or until disease progression (ie, Treatment Phase). Dose modification provisions are provided in the study protocol. Note: temporary withholding of study drug for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. Refer to Section 8.1 for more information on assessing disease progression under these circumstances. Assessment for tumor response and progression will be conducted in accordance with the IWCLL 2008 criteria until disease progression. Disease assessments are required every 12 weeks from Week 1 Day 1 through Week 100, and then every 24 weeks *until 5 years on study and then yearly* thereafter for all subjects (including subjects who discontinue from the study due to an AE) until confirmation of disease progression or death, consent withdrawal, or lost to follow-up.

	All subjects who discontinue study drug will have a safety follow-up visit 30 (+ 7) days after the last dose of study *treatment regardless of whether the subject receives* another *anti*cancer therapy *or demonstrates disease progression* within that timeframe. As described above, all subjects who discontinue study drug due to an intolerable AE will be followed on study for disease progression or death (ie, Post-treatment Phase). The Post-disease Progression Phase will begin once a subject has progressive disease confirmed by the IRC. During this phase, subsequent anticancer therapy with start date of therapy, IWCLL indication for treatment initiation, additional malignancy occurrence, and subject survival status will be recorded. The Post-disease Progression Phase will continue until death, lost to follow up, consent withdrawal, or study closure, whichever occurs first.
Population:	Subjects with previously treated CLL with high-risk prognostic factors as defined in the inclusion criteria.
Centers:	Approximately 200 centers in North America, Europe, Australia, and New Zealand.
Key Inclusion Criteria:	1. Men and women ≥ 18 years of age. 2. ECOG performance status of 0 to 2. 3. Diagnosis of CLL that meets published diagnostic criteria (Hallek 2008): 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. Presence of ≥ 5 x 10^9 B lymphocytes/L (5000 µL) in the peripheral blood (at any point since diagnosis) 4. Must have ≥ 1 of the following high-risk prognostic factors: a. Presence of 17p del by central laboratory b. Presence of 11q del by central laboratory 5. Active disease meeting ≥ 1 of the following IWCLL 2008 criteria for requiring treatment: a. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia (hemoglobin < 10 g/dL) and/or thrombocytopenia (platelets < 100,000/µL). b. Massive (ie, ≥ 6 cm below the left costal margin), progressive, or symptomatic splenomegaly c. Massive nodes (ie, ≥ 10 cm in the longest diameter), progressive, or symptomatic lymphadenopathy. d. Progressive lymphocytosis with an increase of > 50% over a 2-month period or a lymphocyte doubling time (LDT) of < 6 months. LDT may be obtained by linear regression extrapolation of

	absolute lymphocyte counts (ALC) obtained at intervals of 2 weeks over an observation period of 2 to 3 months. In subjects with initial blood lymphocyte counts of < 30 X 10^9/L (30,000/μL), LDT should not be used as a single parameter to define indication for treatment. In addition, factors contributing to lymphocytosis or lymphadenopathy other than CLL (eg, infections) should be excluded. e. Autoimmune anemia and/or thrombocytopenia that is poorly responsive to standard therapy. f. Constitutional symptoms documented in the subject's chart with supportive objective measures, as appropriate, defined as ≥ 1 of the following disease-related symptoms or signs: i. Unintentional weight loss ≥ 10% within the previous 6 months before Screening. ii. Significant fatigue (ie, ECOG performance status 2 or worse; inability to work or perform usual activities). iii. Fevers higher than 100.5°F or 38.0°C for 2 or more weeks before Screening without evidence of infection. iv. Night sweats for > 1 month before Screening without evidence of infection. 6. Must have received ≥ 1 prior therapies for CLL. 8. Meet the following laboratory parameters: a. Absolute neutrophil count (ANC) ≥ 750 cells/μL (0.75 x 10^9/L) or ≥ 500 cells/μL (0.50 x 10^9/L) in subjects with documented bone marrow involvement and independent of growth factor support 7 days before assessment. b. Platelet count ≥ 30,000 cells/μL (30 x 10^9/L) without transfusion support 7 days before assessment. Subjects with transfusion-dependent thrombocytopenia are excluded. c. Serum aspartate transaminase (AST/SGOT) and alanine transaminase (ALT/SGPT) ≤ 3.0 x upper limit of normal (ULN). d. Total bilirubin ≤ 1.5 x ULN. e. Estimated creatinine clearance (ie, estimated glomerular filtration rate [eGFR] using Cockcroft-Gault) ≥ 30 mL/min. 9. Able to receive all outpatient treatment, all laboratory monitoring, and all radiologic evaluations at the institution that administers study drug for the entire study. 10. Women who are sexually active and can bear children must agree to use highly effective forms of contraception while on the study and for 2 days after the last dose of acalabrutinib or 90 days after the last dose of ibrutinib,

	whichever is longer. Highly effective forms of contraception are defined in Section 6.2.11. 11. Men who are sexually active and can beget children must agree to use highly effective forms of contraception during the study and for 2 days after the last dose of acalabrutinib or 90 days after the last dose of ibrutinib, whichever is longer. Highly effective forms of contraception are defined in Section 6.2.11. 12. Men must agree to refrain from sperm donation during the study and for 2 days after the last dose of acalabrutinib or 90 days after the last dose of ibrutinib, whichever is longer. 13. Are willing and able to adhere to the study visit schedule, understand and comply with other protocol requirements, and provide written informed consent and authorization to use protected health information. Note vulnerable subjects are not allowed on this protocol (eg, prisoners or institutionalized subjects).
Key Exclusion Criteria:	1. Known central nervous system (CNS) lymphoma or leukemia. 2. Known prolymphocytic leukemia or history of, or currently suspected, Richter's syndrome. 3. 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 daily or equivalent). 4. Prior exposure to ibrutinib or to a B-cell receptor (BCR) inhibitor (eg, Bruton tyrosine kinase [Btk] inhibitors or phosphoinositide-3 [PI3] kinase inhibitors or Syk inhibitors) or a BCL-2 inhibitor (eg, ABT-199). 5. Received any chemotherapy, external beam radiation therapy, anticancer antibodies, or investigational drug within 30 days before first dose of study drug. 6. Corticosteroid use > 20 mg within 1 week before first dose of study drug, except as indicated for other medical conditions such as inhaled steroid for asthma, topical steroid use, or as premedication for administration of study drug or contrast. For example, subjects requiring steroids at daily doses > 20 mg prednisone equivalent systemic exposure daily, or those who are administered steroids for leukemia control or white blood cell count lowering are excluded. 7. Prior radio- or toxin-conjugated antibody therapy. 8. Prior allogeneic stem cell transplant or autologous transplant.

	9. Major surgery within 4 weeks before first dose of study drug. 10. History of prior malignancy except for the following: a. Malignancy treated with curative intent and with no evidence of active disease present for more than 3 years before Screening and felt to be at low risk for recurrence by treating physician. b. Adequately treated lentigo maligna melanoma without current evidence of disease or adequately controlled non-melanomatous skin cancer c. Adequately treated cervical carcinoma in situ without current evidence of disease 11. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or corrected QT interval (QTc) > 480 msec at screening. 12. Unable to swallow capsules or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel or gastric bypass, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction. 13. Uncontrolled active systemic fungal, bacterial, viral, or other infection (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment) or ongoing intravenous anti-infective treatment. 14. Known history of infection with human immunodeficiency virus (HIV). 15. Serologic status reflecting active hepatitis B or C infection. Subjects with hepatitis B core antibody positive who are surface antigen negative or who are hepatitis C antibody positive will need to have a negative polymerase chain reaction (PCR) result before randomization. Those who are hepatitis B surface antigen positive or hepatitis B PCR positive and those who are hepatitis C PCR positive will be excluded. 16. History of stroke or intracranial hemorrhage within 6 months before randomization. 17. History of bleeding diathesis (eg, hemophilia, von Willebrand disease). 18. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) within 7 days of first dose of study drug. 19. Requires treatment with a strong cytochrome P450 3A (CYP3A) inhibitor/inducer.

	20. Requires treatment with proton-pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole) 21. Breastfeeding or pregnant. 22. Concurrent participation in another therapeutic clinical trial. 23. Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before screening
Primary Endpoint for Final Analysis:	The primary endpoint of the study is PFS. The primary hypothesis is acalabrutinib is non-inferior to ibrutinib with respect to PFS as assessed by IRC review per IWCLL 2008 criteria.
Secondary Endpoints:	To compare between acalabrutinib and ibrutinib in terms of: • Incidence of Grade ≥ 3 infections • Incidence of Richter's transformation • Incidence of atrial fibrillation • OS
Safety Endpoints:	• Frequency, severity, and relatedness of AEs • Frequency of AEs requiring discontinuation of study drug or dose reductions • Change in laboratory assessments
Exploratory Endpoints:	CCI [redacted]

	CCI [redacted]
Study Treatment:	**Acalabrutinib 100 mg Twice per Day (Treatment Arm A):** Acalabrutinib is provided as 100-mg hard gelatin capsules. Acalabrutinib 100 mg will be orally administered twice per day (BID). Doses will be administered 12 hours apart with a window of ± 1 hour. Acalabrutinib will be administered daily until disease progression or unacceptable toxicity. **Ibrutinib 420 mg Once per Day (Treatment Arm B):** Commercially available ibrutinib supplied as hard gelatin capsules *or tablets* (140-mg strength) for oral administration will be administered per the IMBRUVICA approved label. Ibrutinib 420 mg (3 capsules *or tablets*) will be orally administered once per day (QD). Ibrutinib will be administered until disease progression or unacceptable toxicity
Concomitant Therapy and Clinical Practice:	**Permitted Concomitant Therapy:** Standard supportive care medications are permitted. Use of hematopoietic growth factors is permitted per the American Society of Clinical Oncology (ASCO) guidelines. **Prohibited Concomitant Therapy:** Any chemotherapy, anticancer immunotherapy, corticosteroids (at dosages equivalent to prednisone > 20 mg/day), warfarin or equivalent vitamin K antagonists, experimental therapy, and radiotherapy are prohibited. **Acalabrutinib and Concomitant Therapy:** The effect of agents that reduce gastric acidity (eg, proton-pump inhibitors, H2-receptor antagonists or antacids) on acalabrutinib absorption was evaluated in a healthy volunteer study (ACE-HV-004). Results from this study indicate that subjects should avoid the use of calcium carbonate containing drugs or supplements (eg, antacids and calcium supplements) for a period of at least 2 hours before and after taking acalabrutinib. Subjects should also avoid the use of H2-receptor antagonists for a period at least 2 hours before and after taking acalabrutinib. Use of omeprazole or esomeprazole or lansoprazole (or any other proton-pump inhibitors) while taking acalabrutinib is not recommended as it may lower acalabrutinib exposure. Concomitant administration of strong CYP3A inhibitors/inducers and acalabrutinib should be avoided, when possible.
Safety Plan:	An independent Data Monitoring Committee (DMC), chaired by a physician with expertise in CLL, will monitor the safety of the subjects in this study.

	An early safety analysis will be performed after approximately 50 subjects have been treated for approximately 8 weeks. This analysis will focus on deaths, treatment discontinuations, serious adverse events (SAEs), and Grade 3/4 AEs as well as special events of interest. The Medical Monitor will review, in a blinded fashion, this information on an ongoing basis until this early safety analysis is conducted. Detailed information on the role of the DMC and frequency of meetings will be provided in the DMC charter separate from this protocol.
Statistical Methods and Data Analysis:	All efficacy analyses will be performed using the intent-to-treat (ITT) population. **<u>Primary Efficacy Analysis:</u>** The primary efficacy endpoint is PFS, which is defined as the time from the date of randomization until disease progression (assessed by the IRC per IWCLL 2008 criteria) or death from any cause, whichever occurs first. The primary analysis is event-based and will be conducted after enrollment is completed and approximately 250 *IRC-assessed* events have occurred. The primary analysis for this study will be conducted to assess whether acalabrutinib is non-inferior *(NI)* to ibrutinib with respect to PFS. The two-sided 95% confidence interval (CI) for the hazard ratio (HR) of acalabrutinib versus ibrutinib *will be estimated using a stratified Cox regression model.* *The upper bound of the 95% CI for HR will be compared with NI bound of calculated.* **<u>Secondary Endpoints and Analysis:</u>** If acalabrutinib is shown non-inferior to ibrutinib, the secondary endpoints will be tested in a manner that maintains the Type I error rate at ≤ 5%. The incidences of treatment-emergent Grade ≥ 3 infections, Richter's transformation and atrial fibrillation will be summarized and compared between the 2 treatment arms using 2-sided Cochran-Mantel-Haenszel tests adjusted for the randomization strata. Differences between the treatment arms in OS will be assessed using Kaplan-Meier methods and a stratified log-rank test. The OS HR and its 95% CI will be presented using a stratified Cox regression model. *The Statistical Analysis Plan (SAP) will describe the methodology to be used for multiplicity adjustment.* **<u>Safety Analysis:</u>** Detailed tabulations of safety data (AEs and clinical laboratory tests) will be provided for all subjects receiving ≥ 1 dose of study

	drug. The number and percent of subjects with treatment-emergent AEs (TEAEs) will be summarized. Summary of other safety parameters by treatment group will be provided where appropriate. **Sample Size:** A recently completed trial that studied PFS in CLL (Byrd 2014) showed that ibrutinib (the reference/comparator drug in Protocol ACE-CL-006) was superior to ofatumumab, a drug approved for the treatment of CLL in patients with previously treated CLL. Superiority in that study was shown in the overall study population (HR=0.21) as well as in patients with 17p del (HR=0.25) or 11q del (HR=0.14). Protocol ACE-CL-006 is designed to have 80% power to show that the upper bound of a 2-sided 95% CI for PFS is < 1.429 (the NI bound). With randomization in a 1:1 ratio, the trial will require approximately 250 events if acalabrutinib and ibrutinib are truly equally effective. Assuming an enrollment period of about CCI and a follow-up period of approximately CCI after the last subject enters the study, the estimated sample size is 500 subjects (250 per arm).

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LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
11q del	chromosome deletion 11q22.3
17p del	chromosome deletion 17p13.1
ACP-196	acalabrutinib
ADCC	antibody-dependent cell-mediated cytotoxicity
AE(s)	adverse event(s)
AESI	*adverse events of special interest*
AIHA	autoimmune hemolytic anemia
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HBc	hepatitis B core antibody
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{0-12}	area under the plasma concentration-time curve from time 0 to the 12-hour time point
AUC_{0-24}	area under the plasma concentration-time curve from time 0 to the 24-hour time point
AUC_{0-inf}	area under the plasma concentration-time curve from time 0 to infinity
BCR	B-cell receptor
BID	twice per day
Btk	Bruton tyrosine kinase
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practices
CI	confidence interval
CL/F	oral clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed drug concentration
CNS	central nervous system
CCI	[redacted]
CRF	case report form

CCI	
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CVA	*cerebrovascular accident*
CYP	cytochrome P450
DLBCL	diffuse large B cell lymphoma
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DMSO	dimethyl sulfoxide
DOL	*duration of lymphocytosis*
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eGFR	estimated glomerular filtration rate
EGFR	epidermal growth factor receptor
EMEA	European Medicines Agency
CCI	
ET	early termination
CCI	
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDPE	high-density polyethylene
hERG	human ether-à-go-go-related gene
HIV	human immunodeficiency virus
HR	hazard ratio
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation

IEC	Independent Ethics Committee
Ig	immunoglobulin
IgVH	immunoglobulin heavy-chain variable
ILD	*interstitial lung disease*
ITP	idiopathic thrombocytopenia purpura
IRB	Institutional Review Board
IRC	Independent Review Committee
ITT	Intent-to-treat
IV	intravenous
IVIG	intravenous immunoglobulins
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
IWRS	Interactive Web Response System
LDH	lactate dehydrogenase
LDT	lymphocyte doubling time
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
CCI	[redacted]
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NDA	New Drug Application
NHL	non-Hodgkin lymphoma
NI	non-inferiority
NK	natural killer (cells)
CCI	[redacted]
CCI	[redacted]
OS	overall survival
PCR	polymerase chain reaction
PD	pharmacodynamics
PFS	progression free survival
PI3	phosphoinositide-3 (kinase)
PK	pharmacokinetics
PML	progressive multifocal leukoencephalopathy
CCI	[redacted]

CCI	
QD	once per day
QM	every month
QTc	corrected QT interval
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SD	stable disease or standard deviation
SEM	standard error of mean
SFU	safety follow-up
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	half life
TEAE(s)	treatment-emergent adverse events
T_{max}	time to maximum drug concentration
ULN	upper limit of normal
Vz/F	volume of distribution
WBC	white blood cell (count)

1 BACKGROUND INFORMATION

1.1 BTK INHIBITION FOR THE TREATMENT OF CLL

Chronic lymphocytic leukemia (CLL) is a malignancy of B cells that predominantly affects the older population. Chemoimmunotherapy, in particular the combination of purine analogs (eg, 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).

In February 2014, ibrutinib (IMBRUVICA®) monotherapy, the first Btk inhibitor developed for clinical use, was awarded marketing approval in the United States for the treatment of patients with CLL who have had ≥ 1 prior therapy or 17p del. Approval in Europe was in October 2014 with an indication for the treatment of patients with CLL who have received ≥ 1 prior therapy or as first-line therapy in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemoimmunotherapy. These approvals for ibrutinib were based on data from single-arm Phase 2 studies (PCYC 1102/1103) and the randomized Phase 3 study (RESONATE) (IMBRUVICA package insert). In the RESONATE study, which had a median follow up of 9.4 months, ibrutinib demonstrated improvement in PFS (HR=0.21 all patients; HR=0.25 for 17p del; HR=0.14 for 11q del), OS (HR=0.43) and ORR (42.6% vs 4.1%) compared with an active comparator, ofatumumab as adjudicated by the IRC. The progression and survival benefits seen with ibrutinib treatment were demonstrated in all subgroup analyses including patients with high-risk cytogenetic factors (Byrd 2014). Longer follow up on the PCYC 1102/1103 study shows the median PFS has not been reached with 30 months of ibrutinib treatment as assessed by investigators (Brown 2014). However, subgroup analyses suggest patients with 17p deletion (17p del) had the shortest duration of response on ibrutinib treatment with a median duration of response of 27 months by investigator assessment (O'Brien 2014a).

The considerable efficacy observed with ibrutinib is tempered by important safety risks and adverse reactions of interest. The following adverse reactions have been reported for ibrutinib (IMBRUVICA package insert):

- Fatal and non-fatal infections: 25% of patients with mantle cell lymphoma (MCL) and 26% of patients with CLL had infections Grade ≥ 3.
- Atrial fibrillation and atrial flutter in 6% to 9% of all patients.
- Second primary malignancies in 3% to 16% of all patients.
- Major hemorrhages, which include Grade ≥ 3 bleeding (eg, subdural hematomas, gastrointestinal bleeding, hematuria and post-procedural bleeding), in 6% of all patients.
- Diarrhea: 51% of patients with MCL and 63% of patients with CLL had diarrhea, including 4% to 5% Grade 3 or 4 diarrhea.

As mentioned previously, patients with 17p del have the poorest outcome on ibrutinib treatment. Of particular note is newly emerging clinical data suggesting a high rate of Richter's transformation with ibrutinib treatment. O'Brien and colleagues (O'Brien 2014b) report 7.6% (11/144) of patients with 17p del developed Richter's transformation with a median of 13 months of follow-up, with 7 of these cases occurring within the first 24 weeks of ibrutinib treatment.

Chemical optimization, pharmacologic characterization, and toxicologic evaluation have led to identification of ACP-196 (also known as acalabrutinib), an orally bioavailable, new chemical entity that covalently inhibits Btk and shows encouraging activity and acceptable safety in nonclinical studies. Within the class of Btk inhibitors, acalabrutinib is a more selective inhibitor of Btk than ibrutinib. An improved kinase selectivity profile for acalabrutinib may translate to pharmacologic benefits as outlined below:

- Ibrutinib is a potent covalent inhibitor of the epidermal growth factor receptor (EGFR); acalabrutinib is not (Section 1.2.2).
- Ibrutinib is a potent covalent inhibitor of Itk kinase. As such, ibrutinib interferes with natural killer (NK) cell-mediated function and anti-tumor 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 (Section 1.2.4) or antitumor activities of therapeutic CD20 antibodies (Rajasekaran 2014).
- Ibrutinib is also a potent covalent inhibitor of Txk kinase. Itk and Txk kinases regulate the development of cytotoxic $CD8^+$ T cells (Atherly 2006) and modulate interferon gamma 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 and in vitro T-cell studies show reduced $CD8^+$ T cell viability with ibrutinib treatment compared with acalabrutinib (Acerta data on file). The differential potency of acalabrutinib vs 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.

- Ibrutinib is associated with bleeding events in patients. 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 (Section 1.2.5).

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

This Phase 3 study will investigate whether acalabrutinib is non-inferior to ibrutinib, based on centrally determined, independently reviewed PFS, in subjects with previously treated CLL and high-risk prognostic factors (eg, 17p del and 11q del). In addition, the study aims to evaluate safety, tolerability and efficacy, by standard response criteria (Cheson 2012, Hallek 2008), of acalabrutinib compared with ibrutinib.

1.2 PRECLINICAL STUDIES

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

1.2.1 CCI

CCI

1.2.2 Mechanism of Action of Acalabrutinib

Acalabrutinib was specifically designed to be a more potent and selective inhibitor of Btk to avoid off-target side effects 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.

1.2.3 Dog Lymphoma Study

Spontaneous canine B-cell lymphoma shares many characteristics with human non-Hodgkin lymphoma (NHL), including diagnostic classifications and response to Btk inhibition

(Honigberg 2010). The life expectancy in untreated animals with aggressive disease is ~6 weeks, thus enabling rapid assessment of drug efficacy (Vail 2004). Acalabrutinib is currently being evaluated in an ongoing study in canine spontaneous B-cell lymphoma. Fourteen dogs, all of which had diffuse large B-cell lymphoma (DLBCL) confirmed by histology, have been treated with acalabrutinib for at least 2 weeks. The dosages have ranged from 2.5 to 20 mg/kg QD or BID. To date, per Veterinary Cooperative Oncology Group criteria for assessment of response in peripheral nodal lymphoma (Vail 2010), PRs been observed in 4 of 14 dogs (29%) and stable disease (SD) have been observed in 8 of 14 dogs (57%). No acalabrutinib-related AEs have been reported to date in this study. These findings are preliminary and similar to the clinical responses observed with ibrutinib in dogs with spontaneous B-cell lymphoma (Honigberg 2010).

Preliminary results assessing Btk occupancy using a biotin-tagged analogue of acalabrutinib show near complete Btk occupancy over 24 hours with BID dosing in canine tumor tissue (Table 1-1).

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

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

BID = twice per day; Btk = Bruton tyrosine kinase; QD = once per day

1.2.4 Acalabrutinib and Antibody-dependent Cell-mediated Cytotoxicity

Acalabrutinib is not a potent inhibitor of Itk kinase in contrast to ibrutinib. Itk kinase is required for FcR-stimulated NK cell function including calcium mobilization, granule release (Khurana 2007), and overall antibody-dependent cell-mediated cytotoxicity (ADCC). As anti-CD20 antibodies like rituximab are standard of care drugs, often as part of combination regimens, for the treatment of $CD20^+$ B-cell malignancies, the potential of ibrutinib or acalabrutinib to antagonize ADCC was evaluated in vitro. We hypothesized that Btk inhibitor, acalabrutinib, which does not have activity against Itk, may preserve NK cell function and therefore synergize rather than antagonize rituximab-mediated ADCC. Briefly, rituximab-dependent NK-cell mediated cytotoxicity was assessed using lymphoma cell lines as well as

autologous CLL tumor cells. In vitro NK cell cytokine secretion, degranulation and cytotoxicity were assessed by IFN-γ release, CD107a mobilization, and chromium release.

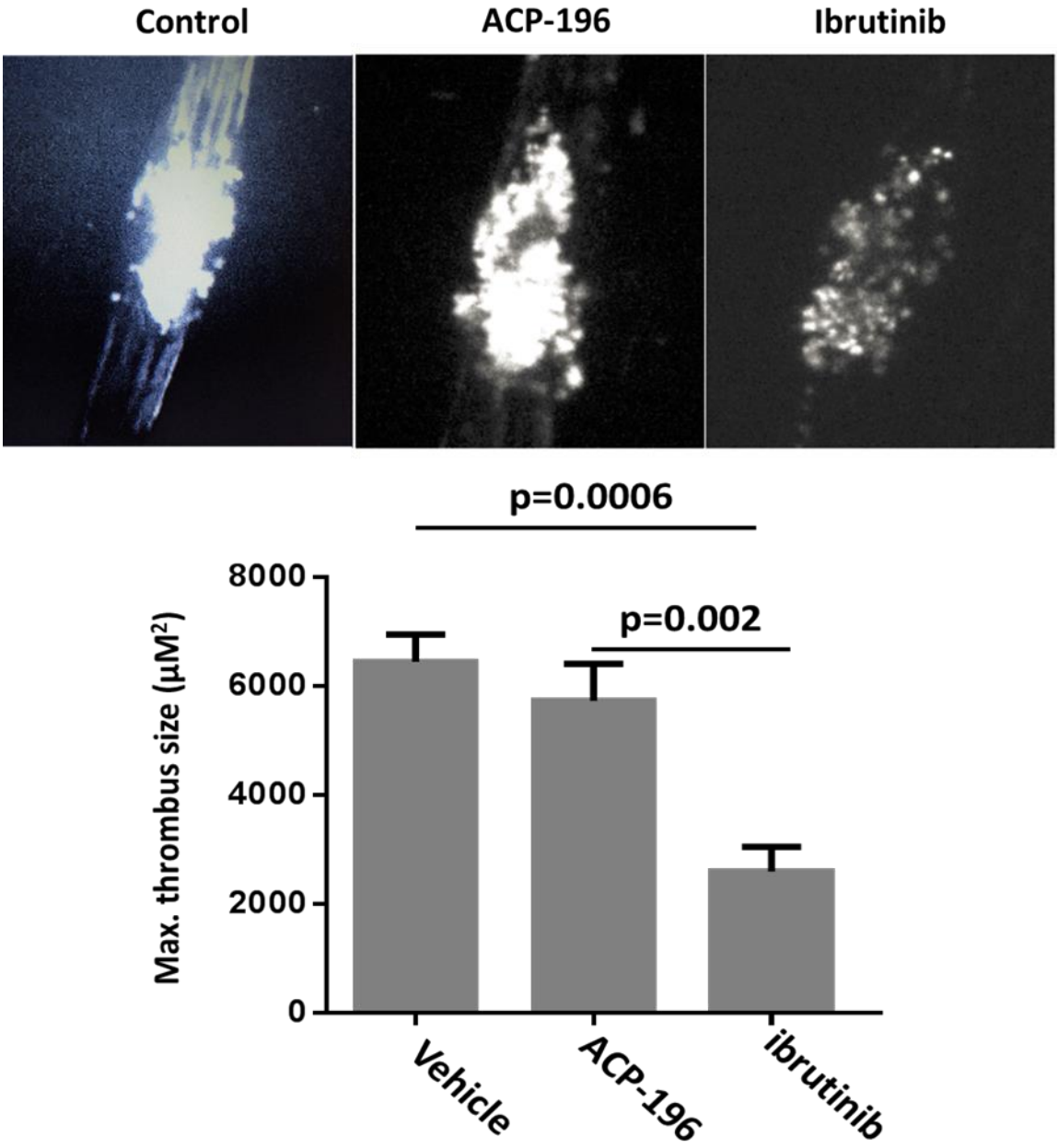
Ibrutinib—in a dose-dependent manner (0.1 and 1 μM)—inhibited rituximab-induced NK cell cytokine secretion (48% p=0.018; 72% p=0.002, respectively). At 1 μM, acalabrutinib did not significantly inhibit cytokine secretion (3.5%). Similarly, acalabrutinib had no inhibitory effect on rituximab-stimulated NK cell degranulation (< 2%) while ibrutinib reduced degranulation by ~50% (p=0.24). At a constant NK:target cell ratio (25:1), 1 μM of ibrutinib, but not acalabrutinib, reduced lysis of chromium-labeled Raji and autologous CLL tumor cells by ~4-fold. Therefore, acalabrutinib resulted in greater in vitro cytotoxicity of rituximab-coated, chromium-labeled lymphoma cells compared with ibrutinib at high NK:target cell ratios. These results suggest acalabrutinib may provide an alternative to ibrutinib for use in combination with antibodies that have ADCC as a mechanism of action.

1.2.5 Acalabrutinib and Thrombus Formation

Ibrutinib is associated with an increased risk of bleeding (Kamel 2015). Hence, the effects of acalabrutinib and ibrutinib were evaluated on human platelet-mediated thrombosis by using the in vivo human thrombus formation in VWF^{HA1} murine model, which has been previously described (Chen 2008). Purified human platelets were preincubated with various concentrations of ibrutinib and acalabrutinib (0.1 μM, 0.5 μM, or 1 μM for each) or dimethyl sulfoxide (DMSO) and then administered to VWF^{HA1} mice followed by laser-induced thrombus formation. Ibrutinib- and acalabrutinib-treated human platelets were fluorescently labeled and infused continuously through a catheter inserted into the femoral artery. Thrombus formation in response to laser-induced vascular injury was monitored in real time using 2-channel confocal intravital microscopy (as described in Furie 2005) (Figure 1-1). Upon induction of arteriole injury untreated platelets rapidly formed thrombi with a mean (± standard error of mean [SEM]) thrombus size of 6,450 ± 292 mm^2. Similarly, acalabrutinib (1 μM) treated platelets formed a slightly smaller, but not significantly different thrombi, with a mean thrombus size of 5733 ± 393 mm^2. In contrast, a significant reduction in thrombus size occurred in platelets pretreated with ibrutinib (1 μM), mean size of 2600 ± 246 mm^2, representing in a reduction in maximal thrombus size by approximately 61% compared with control (P=0.001). Similar results were obtained with platelets pretreated with 500 nM of acalabrutinib or ibrutinib: mean thrombus size of 5946 ± 283 mm^2 and 2710 ± 325 mm^2, respectively. These preliminary results showing reduced thrombus formation for ibrutinib at physiologically relevant concentrations (0.5 to 1 μM) may provide some mechanistic background for the Grade ≥ 3 bleeding events (eg, subdural

hematoma, gastrointestinal bleeding, hematuria and postprocedural hemorrhage) that have been reported ≤ 6% of patients treated with ibrutinib (IMBRUVICA package insert).

Figure 1-1. Effect of Acalabrutinib (1 µM) and Ibrutinib (1 µM) on Thrombus Formation



1.2.6 Safety Pharmacology

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

When screened at 10 µM in binding assays evaluating interactions with 80 known pharmacologic targets such as G-protein-coupled receptors, nuclear receptors, proteases, and ion channels, acalabrutinib shows significant activity only against the A3 adenosine receptor; follow-up dose-response experiments indicated a half-maximal inhibitory concentration (IC_{50}) of 2.7 µM, suggesting a low clinical risk of off-target effects.

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

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

1.2.7 Drug-drug Interaction Potential

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

Please refer to Section 6.3 for guidance on drugs that may cause drug-drug interactions.

1.2.8 In Vivo General Toxicology

The systemic toxicity of acalabrutinib has been investigated in 6 repeat-dose general toxicology studies, 3 with recovery periods, in the rat and the dog. The pivotal GLP studies were two 28-day repeat dose studies in Sprague Dawley rats with 32- and 28-day recovery periods, and a 28-day study in Beagle dogs with a 28-day recovery period. For details on the results of these studies refer to the Investigator Brochure.

1.3 CLINICAL STUDIES

1.3.1 Pharmacokinetics and Pharmacodynamics of Acalabrutinib

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

In Part 1, PK properties of acalabrutinib were evaluated after oral administration of 2 daily divided doses of 2.5 to 50 mg and a single dose of 100 mg. Of the 30 subjects evaluated, all observed systemic concentrations of acalabrutinib. Acalabrutinib plasma time to maximum concentration (T_{max}) values were between 0.5 and 1.0 hour for all dose cohorts and were independent of dose level. The increase in mean maximum observed drug concentration (C_{max}) values was greater than dose proportional based on the increases of C_{max} from the first dose administered. When evaluating AUC_{0-12}, AUC_{0-24} or AUC_{0-inf}, the mean values increased in a dose proportional manner based on the increases of the total dose administered. Mean half-life ($t_{1/2}$) values ranged from 0.97 to 2.1 hours, and appeared to decrease as the dose increased. The mean calculated oral clearance (CL/F: 165 to 219 L/h) and volume of distribution values (Vz/F: 233 to 612 L) appeared to be independent of the dose administered.

Acalabrutinib was not detected in the urine of subjects receiving the 2.5- or 5.0-mg BID doses of acalabrutinib. Acalabrutinib was detected in urine of other subjects (0.4% to 0.6% of dose) and amounts increased in a dose-dependent manner.

In Part 2, the effect of food on the PK of acalabrutinib (75 mg) after a single oral administration was evaluated in 6 men and 6 women. Median acalabrutinib plasma T_{max} values were increased in the fed state (2.5 hours) relative to the fasted state (0.5 hour). The mean plasma acalabrutinib C_{max} fed values decreased to 27.3% of the C_{max} values observed in the fasted state. In contrast, the relative AUC exposure of acalabrutinib remained mostly unchanged in both states. This decrease in exposure in not clinically significant. Therefore, acalabrutinib can be taken without regard to meals.

In Part 3, the effect of itraconazole on the PK of acalabrutinib (50 mg) after a single oral administration was evaluated in 17 subjects. No difference in acalabrutinib T_{max} values was observed in the presence or absence of itraconazole.

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

The PD of acalabrutinib was evaluated using a Btk occupancy assay and correlated with a functional assay that determines the level of Btk inhibition by measuring expression of CD69 and CD86 on B cells. A dose-dependent increase in Btk occupancy and corresponding decrease in CD69/86 expression was observed in this study. Full Btk occupancy (≥ 90%) and complete CD86 and CD69 inhibition (≥ 90%) occurred at the 75- and 100-mg single dosed cohorts 1 to 3 hours after administration. However, only the 100-mg cohort maintained high Btk occupancy (91.5%) and high BCR functional inhibition (CD86: 86 ± 3% and CD69: 78 ± 8%) at 24 hours. For subjects receiving a second dose of acalabrutinib 12 hours after the first administration, full Btk target occupancy was observed 3 hours after the second dose for the 50-mg dosed cohort (Btk occupancy 97 ± 4%).

1.3.2 Clinical Experience of Acalabrutinib in CLL

Acalabrutinib has been administered to participants in clinical studies, including subjects with hematologic malignancies, solid tumors, or rheumatoid arthritis, and participants who are healthy volunteers or with mild to moderate hepatic impairment. No SAEs have been reported in the hepatic impairment study or in the healthy volunteer studies. No expected serious adverse reactions have been identified for acalabrutinib to date. For more detailed information on the clinical experience for acalabrutinib, please refer to the Investigator Brochure.

1.4 SUMMARY AND CONCLUSIONS

This study will evaluate the safety and activity of a potent, second-generation Btk inhibitor, acalabrutinib, versus ibrutinib in subjects with previously treated CLL with high-risk cytogenetics. The design and conduct of this study is supported by an understanding of the natural history and current therapies for subjects with CLL; knowledge of the activity and safety of the first-generation BCR inhibitor (ie, ibrutinib) in subjects with B-cell malignancies; and the available nonclinical and clinical information regarding acalabrutinib. Clinical studies have

shown that acalabrutinib is an orally bioavailable Btk inhibitor with fast absorption and rapid clearance that maintains optimal target coverage over 24 hours with a dosage of 100 mg BID. Acalabrutinib has been well tolerated in healthy volunteers and subjects with CLL or Richter's syndrome. Despite poor prognostic characteristics in the CLL study population, acalabrutinib has induced sustained decreases in lymphadenopathy and provides more rapid reduction and/or resolution of lymphocytosis than ibrutinib. No specific drug-related toxicity has been identified to date for acalabrutinib.

2 STUDY RATIONALE

This randomized controlled Phase 3 study is designed to assess whether acalabrutinib is non-inferior to ibrutinib with respect to PFS in subjects with previously treated CLL who have high-risk prognostic factors per NCCN guidelines (NCCN Version 1.2016).

2.1 DOSE SELECTION RATIONALE FOR ACALABRUTINIB

Preliminary PK data from ACE-CL-001 suggests a plateauing of exposure after 250 mg QD. PD results from this study also suggest Btk resynthesis occurs in malignant B cells within 24 hours. While all dosages evaluated show full Btk occupancy 4 hours after dosing, the 100-mg BID cohort shows full target coverage over 24 hours (≥ 97% Btk occupancy at 4 and 24 hours). Therefore, based on PK/PD and efficacy results of the Phase 1/2 study, acalabrutinib 100 mg BID will be evaluated in this Phase 3 study. This regimen is expected to provide optimal target coverage with lower exposure levels (C_{max}) of acalabrutinib to avoid any potential off-target effects from acalabrutinib.

2.2 NON-INFERIORITY DESIGN AND IBRUTINIB AS COMPARATOR

Assessment of the non-inferiority of acalabrutinib relative to ibrutinib, the reference Btk inhibitor, as therapy for patients with previously treated CLL is the most appropriate approach to describing the therapeutic characteristics of acalabrutinib in this treatment setting. Consistent with increasing scientific discussion regarding comparative effectiveness studies in oncology (Hahn 2012), such a study provides efficacy and safety information that is most relevant to patients, clinicians, regulatory authorities, and health economists in addressing the question of whether the clinical benefit of acalabrutinib can reasonably substitute for that of ibrutinib. The design of such a study offers many strengths that conform to the FDA draft guidance regarding non-inferiority studies (FDA March 2010):

- The benefit:risk of ibrutinib has been established in a large (N=391), well-conducted, randomized, controlled registration study evaluating its therapeutic efficacy relative to

ofatumumab (Byrd 2014, Brown 2014). This pivotal trial of ibrutinib offers a strong foundation upon which to evaluate the non-inferiority (NI) of acalabrutinib.

  - The ibrutinib study showed a large treatment difference in PFS and OS between ibrutinib and an active comparator, thus providing a basis for a non-inferiority margin in the planned trial of acalabrutinib.
  - In the registration study, ibrutinib therapy was associated with a very high ORR (43% to 68% by independent and investigator assessment, respectively), thus providing compelling supportive evidence of drug effectiveness that supplements the ibrutinib treatment effect on PFS.
  - Accrual to the ibrutinib trial occurred between June 2012 and April 2013, ensuring the relevance of the findings to the current practice of oncology and increasing the prospect of a valid constancy assumption between the former ibrutinib trial and the proposed acalabrutinib study.
  - The ibrutinib study data have been subjected to thorough FDA and European Medicines Agency (EMEA) review for product labeling, ensuring the veracity of the results as the basis for considering a new comparative trial with acalabrutinib.

- Ibrutinib and acalabrutinib are covalent inhibitors of Btk and thus offer similar pharmacology as the basis for comparative efficacy and safety.
- The proposed trial addresses the single-agent effects of each drug, thereby avoiding confounding factors that might arise from co-administration of other drugs for the therapy of CLL.
- Due to greater selectivity for Btk inhibition, acalabrutinib may offer a safety profile distinct from ibrutinib that can be directly evaluated in the context of the proposed trial.

The planned NI margin is designed to evaluate the unique benefit:risk profile of an alternative Btk inhibitor**,** while ensuring preservation of substantial benefit of the reference drug, ibrutinib.

2.3 SELECTION OF THE PATIENT POPULATION

The presence of 17p del or 11q del is associated with the worst clinical outcomes in patients with CLL (Gonzalez 2011, NCCN Version 1.2016) with a median survival of < 2 years in the relapsed/refractory setting. Treatment with chemoimmunotherapy for patients with CLL and 17p del is suboptimal (eg, a median PFS of 11.3 months has been reported for front-line fludarabine, cyclophosphamide and rituximab [Hallek 2010]). The recent development of agents targeting BCR signaling has provided substantial improvement in clinical outcome for this aggressive

form of the disease. However, as noted in Section 1.1, patients with 17p del have the poorest outcome on ibrutinib therapy and seem to have a high rate of Richter's transformation.

Study ACE-CL-006 will use eligibility criteria that are substantially similar to those used in the RESONATE study in addition to limiting enrollment to patients with high-risk prognostic factors. This will allow testing of the hypothesis that a more selective Btk inhibitor may lead to greater clinical benefit in high-risk patients including a reduction in the incidence of Richter's transformation.

2.4 BENEFIT/RISK

Acalabrutinib is a potent, orally available small-molecule inhibitor of Btk. In the Phase 1/2 study of acalabrutinib in subjects with CLL or Richter's syndrome (ACE-CL-001), no dose-limiting toxicities (DLTs) have been identified at dosages of ≤ 400 mg QD or 100 to 200 mg BID. To date, no specific drug-related toxicity for acalabrutinib has been identified. The ORR in the evaluable subjects in ACE-CL-001 is currently 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, PK/PD results show the 100-mg BID regimen produces optimal target coverage over 24 hours (ie, more complete coverage of de novo synthesis of Btk), which may provide greater clinical benefit than the QD regimen of ibrutinib.

As described previously, ibrutinib is approved for the treatment of patients with previously treated CLL and patients with CLL with 17p del. The most common adverse reactions (≥ 20%) in patients with CLL treated with ibrutinib are thrombocytopenia, neutropenia, diarrhea, anemia, fatigue, musculoskeletal pain, upper respiratory tract infection, rash, nausea, and pyrexia (IMBRUVICA package insert). Note: For detailed information on the management of these adverse reactions refer to the IMBRUVICA package insert.

3 STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVE

To assess whether acalabrutinib is non-inferior to ibrutinib with respect to PFS, based on IRC assessment, in subjects with relapsed or refractory CLL with high-risk prognostic markers.

3.2 SECONDARY OBJECTIVES

3.2.1 Efficacy Objectives

To evaluate the benefit:risk of acalabrutinib versus ibrutinib in terms of:

- Grade ≥ 3 infections
- Richter's transformation
- Atrial fibrillation
- OS

3.2.2 Safety Objective

The safety and tolerability including adverse events (AEs) of interest and laboratory assessments

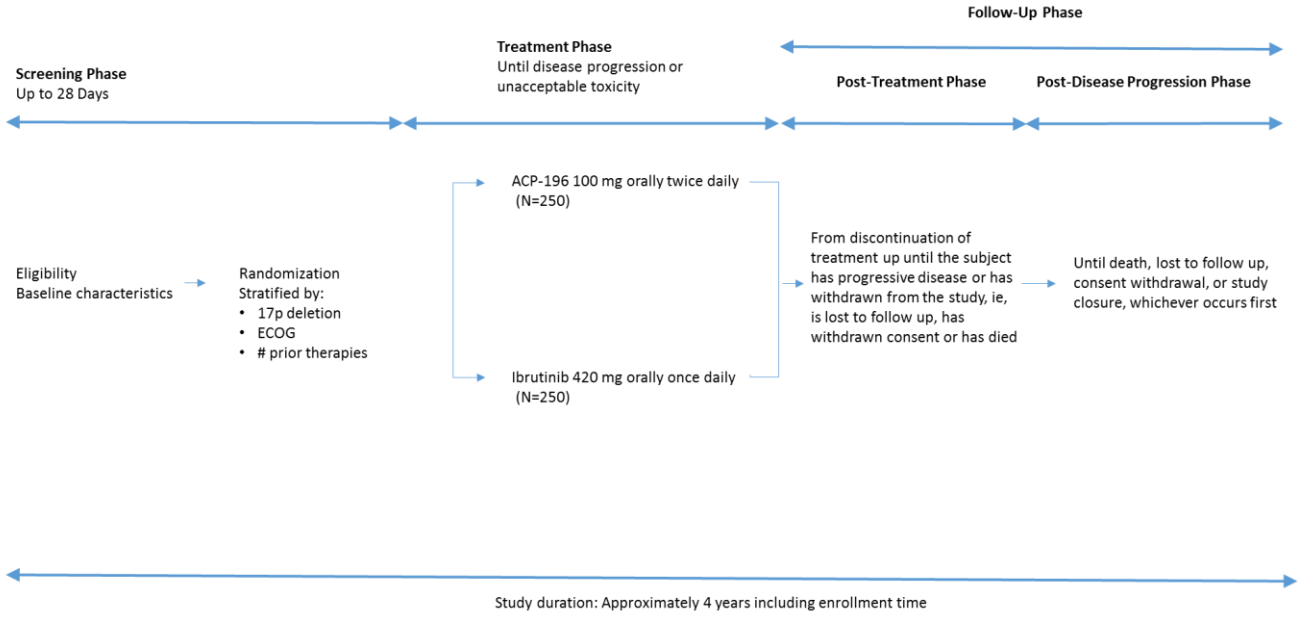
3.2.3 Exploratory Objectives

CCI

4 STUDY DESIGN

This randomized, multicenter (ie, approximately 200 global centers), open-label, non-inferiority Phase 3 study is designed to evaluate the efficacy and safety of acalabrutinib versus ibrutinib in subjects with relapsed or refractory CLL who have high-risk prognostic markers (eg, 17p del and/or 11q del) per NCCN guidelines (NCCN Version 1.2016).

Figure 4-1. Study Schema



Approximately 500 eligible subjects will be randomized in a 1:1 ratio into 2 arms to receive either acalabrutinib 100 mg BID (Arm A; N=250) or ibrutinib 420 mg QD (Arm B; N=250).

This study will use an IWRS for randomization. Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced, and to enhance the validity of statistical comparisons across treatment groups.

Randomization will be performed stratified by the following factors:

- Presence of 17p del
- ECOG performance status (ECOG = 2 versus ECOG ≤1)
- Number of prior therapies (1-3 versus ≥ 4)

Subject participation will include a Screening Phase, a Treatment Phase, a Post-treatment Phase, and a Post-disease Progression Phase. The Screening Phase will last up to 28 days before first dose of study drug, during which the subject's eligibility and baseline characteristics will be determined. The Treatment Phase will last from randomization until study drug discontinuation. Subjects will receive study drug daily until disease progression or unacceptable toxicity. The Post-treatment Phase will follow subjects for disease progression or death, if they

discontinued study drug treatment due to unacceptable toxicity or any reason. Subjects who withdraw consent or are lost to follow will not be followed for disease progression or survival.

The Post-disease Progression Phase will begin once the IRC has confirmed that a subject has progressive disease. In this phase, subsequent anticancer therapy with start date of therapy, IWCLL indication for treatment initiation, additional malignancy occurrence, and subject survival status will be recorded. The Post-disease Progression Phase will continue until death, lost to follow up, consent withdrawal, or study closure, whichever occurs first. Survival status must be assessed, and the date of death must be documented for each subject randomized to treatment, regardless of whether or not the subject received treatment.

Assessment of response and progression will be conducted in accordance with the IWCLL 2008 criteria with the modification that treatment-related lymphocytosis in the absence of other signs or symptoms of disease progression will not be considered progressive disease. The Investigator will evaluate sites of disease by radiologic imaging (primary), physical examination or other procedures as necessary, review of hematology and serum chemistry results, and disease-related symptoms. The same methods of assessment used to assess disease at baseline should be used throughout the study. A central laboratory will perform all hematology testing for the primary endpoint analysis. The primary efficacy analysis will be based on assessment from an IRC. As part of the IRC review, radiographic evaluations assessed by independent central radiologists and hematology results from a central laboratory will be provided. Detailed procedures will be described in a separate charter. An independent DMC will be formed and constituted according to regulatory agency guidelines. Detailed information regarding the composition of the DMC and detailed DMC procedures will be provided in a separate charter. The DMC will review the safety data periodically and provide recommendations according to the charter.

The end of trial is defined as the point when the last subject on study has completed CCI of follow up or has been lost of follow up, whichever occurs first. *In the event that a rollover or safety extension study is available, subjects who remain in this study (Study ACE-CL-006) may be transitioned to such a study. Once all eligible subjects are moved to a rollover or safety extension study, Study ACE-CL-006 would be considered closed. Any subject who would be proposed to move to a rollover or safety extension study would be asked to sign an ICF for the rollover or safety extension study. The rollover or safety extension study would ensure treatment continuation with visit assessments per its protocol.*

5 SELECTION OF SUBJECTS

5.1 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. ECOG performance status of 0 to 2.
3. Diagnosis of CLL that meets published diagnostic criteria (Hallek 2008):
    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. Presence of ≥ 5 x 10^9 B lymphocytes/L (5000 µL) in the peripheral blood (at any point since diagnosis); this applies to CLL only.
4. Must have ≥ 1 of the following high-risk prognostic factors:
    a. Presence of 17p del by central laboratory.
    b. Presence of 11q del by central laboratory.
5. Active disease meeting ≥ 1 of the following IWCLL 2008 criteria for requiring treatment:
    a. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia (hemoglobin < 10 g/dL) and/or thrombocytopenia (platelets < 100,000/µL).
    b. Massive (ie, ≥ 6 cm below the left costal margin), progressive, or symptomatic splenomegaly
    c. Massive nodes (ie, ≥ 10 cm in the longest diameter), progressive, or symptomatic lymphadenopathy.
    d. Progressive lymphocytosis with an increase of > 50% over a 2-month period or a LDT of < 6 months. LDT may be obtained by linear regression extrapolation of ALC obtained at intervals of 2 weeks over an observation period of 2 to 3 months. In subjects with initial blood lymphocyte counts of < 30 X 10^9/L (30,000/µL), LDT should not be used as a single parameter to define indication for treatment. In addition, factors contributing to lymphocytosis or lymphadenopathy other than CLL (eg, infections) should be excluded.
    e. Autoimmune anemia and/or thrombocytopenia that is poorly responsive to standard therapy.
    f. Constitutional symptoms documented in the subject's chart with supportive objective measures, as appropriate, defined as ≥ 1 of the following disease-related symptoms or signs:
        i. Unintentional weight loss ≥ 10% within the previous 6 months before Screening.
        ii. Significant fatigue (ie, ECOG performance status 2 or worse; inability to work or perform usual activities).

iii. Fevers > 100.5°F or 38.0°C for ≥ 2 weeks before Screening without evidence of infection.

iv. Night sweats for > 1 month before Screening without evidence of infection.

6. Must have received ≥ 1 prior therapies for CLL.
8. Meet the following laboratory parameters:
    a. ANC ≥ 750 cells/μL (0.75 x 10^9/L) or ≥ 500 cells/μL (0.50 x 10^9/L) in subjects with documented bone marrow involvement, and independent of growth factor support 7 days before assessment.
    b. Platelet count ≥ 30,000 cells/μL (30 x 10^9/L) without transfusion support 7 days before assessment. Subjects with transfusion-dependent thrombocytopenia are excluded.
    c. Serum AST/SGOT and ALT/SGPT ≤ 3.0 x ULN.
    d. Total bilirubin ≤ 1.5 x ULN.
    e. Estimated creatinine clearance (ie, eGFR using Cockcroft-Gault) ≥ 30 mL/min.
9. Able to receive all outpatient treatment, all laboratory monitoring, and all radiologic evaluations at the institution that administers study drug for the entire study.
10. Women who are sexually active and can bear children must agree to use highly effective forms of contraception while on the study and for 2 days after the last dose of acalabrutinib or 90 days after the last dose of ibrutinib, whichever is longer. Highly effective forms of contraception are defined in Section 6.2.11.
11. Men who are sexually active and can beget children must agree to use highly effective forms of contraception during the study and for 2 days after the last dose of acalabrutinib or 90 days after the last dose of ibrutinib, whichever is longer. Highly effective forms of contraception are defined in Section 6.2.11.
12. Men must agree to refrain from sperm donation during the study and for 2 days after the last dose of acalabrutinib or 90 days after the last dose of ibrutinib, whichever is longer.
13. Must be willing and able to adhere to the study visit schedule, understand and comply with other protocol requirements, and provide written informed consent and authorization to use protected health information (in accordance with national and local patient privacy regulations). Note vulnerable subjects, as defined in the International Conference on Harmonisation (ICH) GCP, are not allowed on this protocol (eg, prisoners or institutionalized subjects).

5.2 EXCLUSION CRITERIA

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

1. Known CNS lymphoma or leukemia.
2. Known prolymphocytic leukemia or history of, or currently suspected, Richter's syndrome.
3. Uncontrolled AIHA or ITP defined as declining hemoglobin or platelet count secondary to autoimmune destruction within the screening period or requirement for high doses of steroids (> 20 mg daily of prednisone daily or equivalent).

4. Prior exposure to ibrutinib or to a BCR inhibitor (eg Btk or PI3 kinase or Syk inhibitors) or a BCL-2 inhibitor (eg, ABT-199).
5. Received any chemotherapy, external beam radiation therapy, anticancer antibodies, or investigational drug within 30 days before first dose of study drug.
6. Corticosteroid use > 20 mg within 1 week before first dose of study drug, except as indicated for other medical conditions such as inhaled steroid for asthma, topical steroid use, or as premedication for administration of study drug or contrast. For example, subjects requiring steroids at daily doses > 20 mg prednisone equivalent systemic exposure daily, or those who are administered steroids for leukemia control or white blood cell count lowering are excluded.
7. Prior radio- or toxin-conjugated antibody therapy.
8. Prior allogeneic stem cell or autologous transplant.
9. Major surgery within 4 weeks before first dose of study drug.
10. History of prior malignancy except for the following:
    a. Malignancy treated with curative intent and with no evidence of active disease present for more than 3 years before Screening and felt to be at low risk for recurrence by treating physician.
    b. Adequately treated lentigo maligna melanoma without current evidence of disease or adequately controlled non-melanomatous skin cancer
    c. Adequately treated cervical carcinoma in situ without current evidence of disease
11. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or QTc > 480 msec at screening.
12. Unable to swallow capsules or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel or gastric bypass, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.
13. Uncontrolled active systemic fungal, bacterial, viral, or other infection (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment) or ongoing intravenous anti-infective treatment.
14. Known history of infection with HIV.
15. Serologic status reflecting active hepatitis B or C infection. Subjects with hepatitis B core antibody positive who are surface antigen negative or who are hepatitis C antibody positive will need to have a negative polymerase chain reaction (PCR) result before randomization. Those who are hepatitis B surface antigen positive or hepatitis B PCR positive and those who are hepatitis C PCR positive will be excluded.
16. History of stroke or intracranial hemorrhage within 6 months before randomization.
17. History of bleeding diathesis (eg, hemophilia, von Willebrand disease).
18. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) within 7 days of first dose of study drug.
19. Requires treatment with a strong CYP3A inhibitor/inducer.

20. Requires treatment with proton-pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole).
21. Breastfeeding or pregnant.
22. Concurrent participation in another therapeutic clinical trial.
23. Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before screening

6 DOSAGE AND ADMINISTRATION

6.1 IDENTIFICATION OF INVESTIGATIONAL PRODUCT

6.1.1 Acalabrutinib

Acalabrutinib is provided as hard gelatin capsules for oral administration. The capsules are packaged in opaque high-density polyethylene (HDPE) plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies. The drug product is manufactured for Acerta Pharma by a contract manufacturer. All formulation excipients are compendial and are commonly used in oral formulations.

Refer to the Investigator Brochure for additional information regarding the drug product to be used in this study.

6.1.2 IMBRUVICA (Ibrutinib)

This study will use commercially available ibrutinib. The Sponsor will either directly supply sites with ibrutinib or the sites will be reimbursed to prescribe ibrutinib; this will be detailed separately in each site's clinical trial agreement.

Ibrutinib is provided as 140-mg capsules *or tablets*. Refer to IMBRUVICA approved label for details.

6.2 DRUG PREPARATION AND ADMINISTRATION

6.2.1 Acalabrutinib

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

Acalabrutinib is intended to be administered orally BID (with the second daily dose 11 to 13 hours after first dose) with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in liquid.

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

6.2.2 Assessment of Toxicity

The evaluation of potential treatment-induced toxicity in subjects with advanced CLL may be quite difficult requiring careful consideration of the manifestations of the underlying disease, as well as adverse reactions to the therapy under study. Some of the conventional criteria for toxicity are not applicable especially under circumstances of progressive bone marrow failure from the CLL itself. Dose modifications for hematologic toxicity in subjects with CLL must consider the increased frequency of hematologic compromise at the initiation of therapy. Therefore the standard criteria used for solid tumors are difficult to be applied directly; many subjects would be considered to have Grade 2 to 4 hematologic toxicity at presentation.

As a consequence, dose modification decisions for subjects with cytopenia (below the lower limit of the normal range) at baseline will be based on the IWCLL 2008 grading scale for hematologic toxicity in CLL studies (see Appendix E).

For dose modifications or discontinuation guidance of acalabrutinib in Arm A, see Section 6.2.4. For dose modifications or discontinuation guidance of ibrutinib in Arm B, see Section 6.2.9.

6.2.3 Dose Delays for Acalabrutinib

Treatment with acalabrutinib should be held for any unmanageable, potentially study drug-related toxicity that is Grade ≥ 3 in severity. Any other clinically important events where dose delays may be considered appropriate by the investigator must be discussed with the Medical Monitor. Study drug may be held for a maximum of 28 consecutive days from expected dose due to toxicity. Study treatment should be discontinued in the event of a toxicity lasting > 28 days, unless reviewed and approved by the Medical Monitor.

Note: temporary withholding of study drug for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. Refer to Section 8.1 for more information on assessing disease progression under these circumstances.

6.2.4 Dose Modification and Discontinuation for Acalabrutinib

Treatment-related Lymphocytosis

Treatment-related lymphocytosis is defined as ALC > 5000/μL and an increase above baseline, and is associated with agents known to inhibit BCR (Hallek 2008, NCCN Version 1.2016,

Cheson 2012). Given the known mechanism of action of BCR-inhibiting agents including ibrutinib, treatment-related lymphocytosis is an expected and frequent phenomenon observed with initiation (or re-initiation) of Btk inhibitors. Specifically, the IMBRUVICA approved label states an increase in lymphocyte counts (≥ 50% increase from baseline and above absolute lymphocyte count of 5,000/μL) occurred in 77% of subjects (N=195) in the pivotal Phase 3 CLL study. The onset of lymphocytosis occurred during the first month of ibrutinib therapy and resolved by a median of 23 weeks (range: 1 to 104+ weeks). Asymptomatic treatment-related lymphocytosis should not be considered an AE and subjects should remain on study treatment. A high number of circulating malignant cells (≥ 400,000/μL) may confer increased risk; these subjects should be closely monitored. Administer supportive care such as hydration and/or leukophoresis as indicated. Acalabrutinib may be temporarily held and the Medical Monitor should be contacted.

The actions in Table 6-1 should be taken for the following toxicities:

- Grade 4 ANC (< 500/μL) for > 7 days (Neutrophil growth factors are permitted per 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 6-1. Drug Discontinuation Actions for Acalabrutinib

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

Any changes to the dosing regimen must be recorded in the Dosage Administration CRF.

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.

Any changes to the dosing regimen must be recorded in the Dosage Administration CRF.

6.2.5 Risks Associated with Acalabrutinib Treatment

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

6.2.5.1 Reference Safety Information

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

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

6.2.5.2 Hemorrhage

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

Patients receiving *antithrombotic agents* may be at increased risk of hemorrhage. *Use caution with antithrombotic agents and consider additional* monitor*ing* 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.

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

6.2.5.3 Infections

Serious infections (bacterial, viral, and fungal), including fatal events, have occurred in clinical studies with acalabrutinib. The most frequent reported Grade ≥3 infection was pneumonia (preferred term).

Consider prophylaxis in subjects who are at increased risk for opportunistic infections. Subjects should be monitored for signs and symptoms of infection and treated as medically appropriate. Refer to Section 6.2.5.3.1 and Section 7.1 for additional information and monitoring guidance for viral hepatitis and Section 6.2.5.3.2 for additional information and management guidance for signs and symptoms of PML.

6.2.5.3.1 HEPATITIS B VIRUS REACTIVATION

Cases of hepatitis B virus (HBV) reactivation have *occurred* in *clinical studies* with acalabrutinib. Therefore, subjects who are hepatitis B core antibody (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 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. Insufficient data exist regarding the safety of resuming acalabrutinib in subjects who develop HBV reactivation.

6.2.5.3.2 PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

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

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

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

If PML is confirmed, permanently discontinue acalabrutinib.

6.2.5.4 Cytopenias

Grade 3 or 4 events of cytopenias, including neutropenia, anemia, and thrombocytopenia have occurred in patients treated with acalabrutinib. Monitor blood counts as specified in the schedule of assessments and as medically appropriate. Please refer to Sections 6.2.3 and 6.2.4 for study drug modification guidance. Patients with cytopenias should be managed according to institutional guidelines or as clinically indicated.

6.2.5.5 Second Primary Malignancies

Second primary malignancies, *including solid tumors and skin cancers*, have been reported in subjects treated with acalabrutinib. The most frequent second primary malignancy was skin cancer (basal cell carcinoma). *Subjects should be monitored for signs and symptoms of malignancy. Subjects who develop a second primary malignancy* should be managed

according to institutional guidelines *with diagnostic evaluations* as clinically indicated, *and it may be necessary for subjects to permanently discontinue study treatment. Continuation of acalabrutinib treatment should be discussed with the medical monitor. Refer to Section 7.2.2.4 for second primary malignancy reporting guidance.*

6.2.5.6 Atrial Fibrillation

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

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

6.2.6 IMBRUVICA (Ibrutinib)

Refer to the United States IMBRUVICA approved label as a reference; refer to country-specific labels for detailed product information, dosage and administration, dose interruptions and modifications, and precautions and adverse reactions.

6.2.7 Dosage Regimen and Administration for Ibrutinib

Ibrutinib 420 mg is taken QD (three 140-mg capsules *or tablets* once daily). Capsules *or tablets* should be taken orally with 8 ounces (approximately 240 mL) of water (avoid grapefruit juice and Seville orange juice due to CYP3A inhibition). The capsules *or tablets* should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water.

6.2.8 Dose Delays for Ibrutinib

Treatment with ibrutinib should be held for any unmanageable, potentially study drug-related toxicity that is Grade ≥ 3 in severity. Any other clinically important events where dose delays may be considered appropriate by the investigator must be discussed with the Medical Monitor. Study drug may be held for a maximum of 28 days from expected dose due to toxicity. Study treatment should be discontinued in the event of a toxicity lasting > 28 days, unless reviewed and approved by the Medical Monitor.

Note: temporary withholding of study drug for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. Refer to Section 8.1 for more information on assessing disease progression under these circumstances.

6.2.9 Dose Modification and Discontinuation for Ibrutinib

The actions in Table 6-2 should be taken for the following toxicities:

- Grade 4 ANC (< 500/μL) for > 7 days (Neutrophil growth factors are permitted per ASCO guidelines [Smith 2015] and use must be recorded on the 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 6-2. Dose Discontinuation Actions for Ibrutinib

Occurrence	Action
1st	Hold ibrutinib until recovery to Grade ≤ 1 or baseline; may restart at original dose level (420 mg daily)
2nd	Hold ibrutinib until recovery to Grade ≤ 1 or baseline; may restart at 280 mg daily
3rd	Hold ibrutinib until recovery to Grade ≤ 1 or baseline; may restart at 140 mg daily
4th	Discontinue ibrutinib

Any changes to the dosing regimen must be recorded in the Dosage Administration CRF.

Note: If local regulations require following local prescribing information for dose modifications/discontinuation, and they differ from the aforementioned, then the local regulations should be followed.

6.2.10 Risks Associated with Ibrutinib Treatment

Refer to the IMBRUVICA approved label for precautions including information on withholding ibrutinib 3 to 7 days before and after surgery and treatment-related lymphocytosis. In addition, the following warnings and precautions apply to ibrutinib treatment:

6.2.10.1 Hemorrhage

Grade ≥ 3 bleeding events (intracranial hemorrhage, subdural hematoma, gastrointestinal bleeding, hematuria and postprocedural hemorrhage) have occurred in ≤ 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half the patients treated with ibrutinib.

6.2.10.2 Infections

Fatal and non-fatal infections have occurred with ibrutinib therapy. Twenty-five percent of patients with MCL and 26% of patients with CLL had infections Grade ≥ 3.

6.2.10.2.1 HEPATITIS B VIRUS REACTIVATION

Cases of hepatitis B virus (HBV) reactivation have been observed in post-approval use of ibrutinib. Therefore, 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 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. Insufficient data exist regarding the safety of resuming ibrutinib in subjects who develop HBV reactivation.

6.2.10.3 Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias, including neutropenia (range, 23% to 29%), thrombocytopenia (range, 5% to 17%), and anemia (range, 0% to 9%), occurred in patients treated with ibrutinib.

6.2.10.4 Atrial Fibrillation

Atrial fibrillation and atrial flutter (range, 6% to 9%) have occurred in patients treated with ibrutinib, particularly in patients with cardiac risk factors, acute infections, and a previous history of atrial fibrillation.

6.2.10.5 Hypertension

Hypertension has occurred in 6% to 17% of patients treated with ibrutinib with a median time to onset of 4.6 months (range: 0.03 to 22 months).

6.2.10.6 Second Primary Malignancies

Other malignancies (range: 3% to 16%) including non-skin carcinomas (range: 1% to 4%) have occurred in patients treated with ibrutinib. The most frequent second primary malignancy was nonmelanoma skin cancer (range: 2% to 13%).

6.2.10.7 Tumor Lysis Syndrome

Tumor lysis syndrome has been reported with ibrutinib therapy. Monitor patients closely and take appropriate precautions in patients at risk for tumor lysis syndrome (eg, high tumor burden).

6.2.10.8 Cerebrovascular Accidents

Cases of cerebrovascular accident (CVA), transient ischemic attack, and ischemic stroke including fatalities have been reported with the use of ibrutinib, with and without concomitant atrial fibrillation and/or hypertension. Monitor patients closely for signs and symptoms compatible with CVA events.

6.2.10.9 Interstitial Lung Disease

Cases of interstitial lung disease (ILD) have been reported in patients treated with IMBRUVICA. Monitor patients for pulmonary symptoms indicative of ILD.

6.2.10.10 Leukostasis

Cases of leukostasis have been reported in patients treated with IMBRUVICA. A high number of circulating lymphocytes (>400,000/mcL) may confer increased risk.

6.2.10.11 Embryo-fetal Toxicity

Based on findings in animals, ibrutinib can cause fetal harm when administered to a pregnant woman.

6.2.11 Reproductive Toxicity

Definition of Women of Non-reproductive Potential:

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

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

OR

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

OR

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

Highly Effective Methods of Contraception[‡]

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

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

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

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

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

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.

Women who are sexually active and can bear children (see definition above) must agree to use highly effective forms of contraception during the study and for 2 days after the last dose of acalabrutinib or 90 days after the last dose of ibrutinib, whichever is longer. Men who are sexually active and can beget children must agree to use highly effective forms of contraception during the study and for 90 days after the last dose of ibrutinib. Men must also refrain from donating sperm during the study and for 90 days after the last dose of ibrutinib.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. To participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period and for 2 days after the last dose of acalabrutinib or 90 days after the last dose of ibrutinib, whichever is longer. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

Subjects should promptly notify the investigator if they, or their partners, become pregnant during this period. *Female subjects must also notify the investigator if they become pregnant within 2 days after the last dose of acalabrutinib.* If a female subject becomes pregnant during the treatment period, she must discontinue study drug immediately. Pregnancy in a female subject or a male subject's partner must be reported as outlined in Section 7.2.2.

6.3 CONCOMITANT MEDICATIONS

6.3.1 Allowed Concomitant Medications

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

Tumor Lysis Syndrome

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

6.3.2 Guideline for Use of CYP Inhibiting/Inducing Drugs

Acalabrutinib

At the systemic exposure levels expected in this study, acalabrutinib inhibition of CYP-mediated metabolism of other drugs is not anticipated. However, acalabrutinib is metabolized in part by CYP3A. In a clinical drug-drug interaction study, co-administration of the potent CYP3A inhibitor, itraconazole, increased the mean plasma exposures of acalabrutinib by about 5-fold (Section 1.3.1). In addition, concomitant administration of a strong inducer of CYP3A, rifampicin, reduced the exposure of acalabrutinib to 23%, relative to acalabrutinib dosed alone. Concomitant administration of strong CYP3A inhibitors/inducers and acalabrutinib should be avoided when possible (see Appendix C for a list of these agents). *Subjects requiring long-term (>1 week) treatment with a strong CYP3A inhibitor/inducer are excluded from the study. In addition, the use of strong CYP3A inhibitors or inducers within 7 days of the first dose of study drug is prohibited. If a subject requires short-term treatment (≤7 days) with a strong CYP3A inhibitor, acalabrutinib treatment should be interrupted. If the subject requires treatment with a moderate CYP3A inhibitor, the acalabrutinib dose should be reduced to 100 mg QD. Co-administration of strong CYP3A inducers should be avoided. If a subject requires treatment with a strong CYP3A inducer, the acalabrutinib dose should be increased to 200 mg BID.*

Ibrutinib

Refer to the section titled “Dose Modifications for Use with CYP3A Inhibitors” in the IMBRUVICA approved label.

6.3.3 Guideline for Use of Drugs that Affect Gastric pH

Acalabrutinib

The effect of agents that reduce gastric acidity (eg, proton-pump inhibitors, H2-receptor antagonists or antacids) on acalabrutinib absorption was evaluated in a healthy volunteer study (ACE-HV-004). Results from this study indicate that subjects should avoid the use of calcium carbonate containing drugs or supplements (eg, antacids and calcium supplements) for a period of at least 2 hours before and after taking acalabrutinib.

Subjects should also avoid the use of H2-receptor antagonists for a period at least 2 hours before and after taking acalabrutinib. Use of omeprazole or esomeprazole or lansoprazole (or any other proton-pump inhibitors) while taking acalabrutinib is not recommended as it may lower acalabrutinib exposure.

Ibrutinib

No specific instructions are provided in the approved label for ibrutinib regarding agents that reduce gastric acidity (*refer to approved label for ibrutinib)*.

6.3.4 Prohibited Concomitant Medications

Any chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy for treating CLL are prohibited if being used to treat the disease initially under study. Short course use of steroids (≤ 2 weeks) > 20 mg/day is permitted for premedication use, or to manage infusion related reactions or to manage other inflammatory reactions, such as asthma exacerbations. High-dose corticosteroids used to treat the 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. Should a subject develop a second primary malignancy while on trial, continuation on trial medication after curative treatment of the second primary malignancy may be considered after discussion with the medical monitor.

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

The concomitant use of strong inhibitors/inducers of CYP3A (see Appendix C) should be avoided when possible (see Section 6.3.2). Concomitant administration of a strong inducer of CYP3A has the potential to decrease exposure of acalabrutinib and could reduce efficacy. For additional information on drugs with potential drug-drug interactions, refer to Section 6.3.

6.4 TREATMENT COMPLIANCE

Subject compliance with acalabrutinib/ibrutinib will be assessed at each study visit. Compliance will be assessed by the investigator and/or study personnel at each visit using direct questioning, examination of subject drug administration diaries, or pill counts.

6.5 DIETARY RESTRICTIONS

Acalabrutinib should be taken with water and may be taken with or without food. Because acalabrutinib is metabolized by CYP3A, subjects should be strongly cautioned against using herbal remedies or dietary supplements (in particular, St. John's wort, which is a potent CYP3A inducer). Otherwise, subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

7 EFFICACY AND SAFETY PROCEDURES

The Schedule of Assessments is provided in Appendix A. Descriptions of the scheduled evaluations are outlined below. *See Appendix K for management of study procedures during pandemic.*

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 efficacy assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. Such assessments will be captured in the protocol-specific electronic database as appropriate. This study will primarily use central laboratory testing for laboratory evaluations. Samples from sites' local laboratories will be used if central testing is unavailable.

Some study centers may choose to provide subjects with clinical trial cards, which provide information about the study and emergency contact details.

7.1 DESCRIPTION OF PROCEDURES

Informed Consent

The subject must read, understand and sign the IRB/IEC-approved informed consent form (ICF) confirming his or her willingness to participate in this study before initiating any screening activity that is not considered standard of care by institutional standards. Subjects must also grant permission to use protected health information if required by local regulations. In addition, subjects must sign all approved ICF amendments per the site IRB/IEC's guidelines during the course of the study.

Confirmation of Eligibility

Perform all necessary procedures and evaluations to document that the subject meets each eligibility criterion (Section 5). Blood samples for hematology and serum chemistry collected at Screening will be evaluated by a central laboratory to confirm eligibility. With the exception of fluorescence in situ hybridization (FISH), if central laboratory results submitted during the screening period are unavailable, the Medical Monitor may review local laboratory results and approve the subject for randomization based on these laboratory values on a case-by-case basis provided another sample is redrawn and submitted before treatment. The following de-identified documentation will be reviewed before enrollment:

- Copies of a pathology report confirming diagnosis of CLL

- Radiology reports from screening CT/MRI documenting measurable nodal disease.
- Copies of bone marrow aspirate and biopsy report.
- Copies of FISH denoting if the subject has 17p del and/or 11q del.

Treatment with study drug should begin within 7 days of randomization.

Medical History

Collect and record the subject's complete history including concurrent medical signs and symptoms, alcohol use and, if a smoker, cigarette use. Disease history, including the date of initial diagnosis, Rai and Binet staging within 28 days of first dose with study drug, documentation of refractory disease, prior anticancer treatments with best responses and progression-free interval to these treatments, and history of autoimmune CLL complications and their treatment will also be recorded based upon available documents and subject history.

Physical Examination

The physical examination includes height (Screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, and lymphatic system. The lymphatic system examination will include bidimensional measurements of palpable lymph nodes and measurement of spleen and liver sizes by centimeters below the costal margin on the respective side. Only physicians, physician assistant, or oncology nurse practitioners should perform the lymphatic system examination. As much as possible, the same person should perform all the lymphatic exams for a given subject.

Disease-related Symptoms

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% of more within the previous 6 months;
b. Significant fatigue (ie 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

Vital signs will include blood pressure, heart rate, respiratory rate, and body temperature.

Electrocardiogram

Subjects should be in supine position and resting for at least 10 minutes before any protocol-specified ECGs.

ECOG Performance Status

The ECOG performance index is provided in Appendix B.

Hepatitis Serologies

Hepatitis serology testing must include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), anti-HBc, and hepatitis C (HCV) antibody. Since intravenous immunoglobulins (IVIG) may cause false positive hepatitis serology, subjects who are receiving prophylactic IVIG and have positive HBsAg or anti-HBc must have negative hepatitis B DNA to be eligible. In addition, any subjects testing positive for any hepatitis serology, must have PCR testing (see Appendix A and exclusion criterion #15). Testing will be done by local or central laboratory.

Refer to Section 6.2.5 and Appendix A regarding monitoring of subjects who are anti-HBc positive.

Cytogenetics and FISH Panel

Screening peripheral blood (required) will be sent to a central vendor to be tested for 17p del, 13q-, +12, 11q- by FISH and stimulated karyotyping.

Genetic and Molecular Prognostic Markers

A blood sample will be collected and analyzed centrally to study the pretreatment prognostic factors. These prognostic factors have previously been associated with disease outcome in CLL subjects.

Immunoglobulin Heavy-chain Variable (IgVH) and p53 Mutational Status

One sample will be collected for IgVH and p53 mutational status.

CD38 and ZAP-70 Leukemia Cell Expression

One sample will be collected to study the leukemia cell expression of CD38 and ZAP-70.

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Pregnancy Test

Serum pregnancy testing per the Schedule of Assessments (Appendix A) will be required only for women with childbearing potential. This test may be performed more frequently if required by local regulatory authorities.

Hematology

Hematology will be evaluated by a central laboratory and will include a complete blood count (CBC) with white blood cell (WBC) differential. Any missing central laboratory blood samples should be redrawn as soon as possible. In the event that the missing central laboratory sample is unrecoverable, local laboratory results will be collected, if available, and entered in the clinical database for response or progression confirmation.

Determination of T/B/NK Cell Count

Whole blood samples will be analyzed for absolute T/B/NK counts (CD3, CD19, CD4, CD8, CD16/56) using a standard cell marker panel. This assay will be performed at the central laboratory on the same blood sample collected for standard hematology.

Serum Chemistry

Serum chemistry will be evaluated by a central laboratory and will include albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen (BUN), calcium, creatinine, glucose, lactate dehydrogenase (LDH), phosphate/phosphorus, potassium, sodium, total bilirubin, and uric acid. Any missing central laboratory blood samples should be redrawn as soon as possible

Serum Immunoglobulins and β_2-microglobulin

Sample(s) will be sent to a central laboratory for quantitative immunoglobulin (Ig) (ie, IgG, IgM, and IgA) levels and serum β2-microglobulin.

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Bone Marrow Aspirate and Biopsy

For Eligibility

A unilateral bone marrow aspirate and biopsy will be done at screening or ≤ 3 months before randomization. The Screening sample must be sent to the central laboratory for analysis.

Subjects who have a bone marrow biopsy done within 3 months of randomization may use these results in lieu of the Screening sample required for this study. If slides (both bone marrow and aspirate) are available, these should be sent to the central laboratory for analysis.

For Response Evaluation (more details provided in Appendix D)

CCI [redacted] In cases where cytopenic progression is suspected, a bone marrow aspirate or biopsy should be performed to distinguish autoimmune and drug-related cytopenias. In cases where Richter's transformation is suspected (eg, rapidly progressive B symptoms; bulky lymphadenopathy; organomegaly; anemia; a low platelet count; and elevated serum LDH, calcium, and β2 microglobulin levels), obtain whole body PET-CT to pinpoint the area for diagnostic biopsy (SUV > 5) (Jain 2012). Confirm diagnosis by biopsy of lymph nodes, bone marrow, or involved organs. Pathology analyses can be done at local laboratories in addition to central laboratory testing for confirmation of Richter's transformation. Bone marrow aspirate and biopsy samples must be sent to the central laboratory for analysis.

CT Scans

Radiologic imaging by computed tomography (CT) with contrast is required and must include the pelvis, abdomen, chest, and neck. 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 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 for imaging assessments if a contrast CT scan is contraindicated or unobtainable (in cases where MRI is desirable, the MRI must be obtained at baseline and at all subsequent response evaluations).

Computed tomography scans will be performed until disease progression is confirmed by the IRC 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. If the sole measurable lesion lies within the field of

prior radiotherapy, there must be evidence of disease progression in that lesion that has not been previously irradiated. *Refer to the Schedule of Assessments (Appendix A) to determine the frequency that CT scans need to be obtained*.

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

A central imaging 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.

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Adverse Events

The accepted regulatory definition for an AE is provided in Section 7.2.1. Important additional requirements for reporting SAEs are explained in Section 7.2.2. *See Section 7.2.2.1 for details regarding adverse event reporting.*

Prior and Concomitant Medications

Document all concomitant medications and procedures from 14 days before the start of study drug administration through 30 days after the last dose of all study drugs, or at documented disease progression, whichever is longer.

After a subject discontinues study treatment, receipt of all subsequent anticancer therapies will be collected.

Routine Clinical Assessments

Routine clinical assessments include physical exams, recording of symptoms, and hematologic evaluations to evaluate for both AEs and for disease progression at times when the CT scan is not obtained. If a subject shows signs of progression, the subject may continue treatment until

progression is confirmed by the IRC. The Investigator should report any suspected disease progression to the Sponsor or designee. Subjects should continue to be followed and adhere to study-related procedures until progression has been confirmed by the IRC regardless of the administration of subsequent anticancer therapy. New anticancer therapy should be withheld if clinically appropriate in the absence of IRC-confirmed progressive disease. In addition, laboratory assessments for disease progression will need to be confirmed by the central laboratory.

Overall Response Evaluations

Overall response assessments will include evaluation of physical exams, 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 exam and a CBC with differential to determine if disease progression is present. 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 exam at least 2 weeks later. In addition, when clinically appropriate, based on investigator perceived risk:benefit assessment, a subject may continue treatment until progression is confirmed by the IRC, unless considered medically contraindicated. New anticancer therapy should be withheld if clinically appropriate in the absence of confirmed progressive disease by the IRC. The blood samples for response or disease progression determination are to be confirmed by a central laboratory (samples from local laboratories can be used if central testing is unavailable).

Early Termination (ET) Visit/Safety Follow-up (SFU) Visit

An ET visit is required for safety assessments for any subjects who permanently discontinue treatment for any reason, including disease progression. The ET visit should be performed within 7 days of the last dose of all study drugs, if possible, and is not required for subjects who discontinue from the study within 10 days of a scheduled study visit or if the ET visit would be performed within 14 days of the SFU visit.

A SFU visit should be conducted at 30 (+ 7) days after his or her last dose of all study drugs 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 time frame. Refer to Appendix A for the assessments required for the ET and SFU visits.

Survival

After progression, subjects will be contacted to assess survival status approximately every 12 weeks until death, withdrawal by subject, lost to follow-up, or study terminated by Sponsor, whichever comes first. At study closure, a survival sweep will be conducted. All subjects who are on study and not known to have died before the survival sweep will be contacted at that time.

Subsequent Anticancer Therapies

After study drug treatment is complete, the following information on subsequent anticancer therapies will be collected approximately every 12 weeks until death, withdrawal by subject, lost to follow-up, or study terminated by Sponsor, whichever comes first:

- Receipt of all subsequent anticancer therapies
- IWCLL indication for initiation of subsequent anticancer therapy
- Response to all subsequent anticancer therapies

7.2 ASSESSMENT OF SAFETY

The safety of this study will be assessed by an independent DMC. All randomized subjects will be evaluated clinically and using standard laboratory testing during their participation in this study. Safety assessments will consist of monitoring and recording AEs and SAEs; measurements of protocol-specified hematology, clinical chemistry, 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).

7.2.1 Definitions

Adverse Events

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational study drug, whether or not considered related to the study drug (FDA Guidance for Industry 1995).

For the purposes of this clinical study, AEs include events which are either new or represent detectable exacerbations of pre-existing conditions.

Disease progression is not an AE; rather it may be the cause of an AE. The clinical diagnosis that is associated with disease progression must be reported as all other AEs. “Disease progression” should never be used as an AE term.

AEs may include, but are not limited to:

- Subjective or objective symptoms spontaneously offered by the subject and/or observed by the Investigator or study staff including laboratory abnormalities of clinical significance (Note: “clinical significance” is defined as requiring change in study drug dose or discontinuation of study drug or any other medical intervention).
- Any AEs experienced by the subject through the completion of final study procedures.
- 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.

The following are NOT considered an AE:

- **Pre-existing condition:** 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 informed consent form is not considered an SAE, but rather a therapeutic intervention. However, if during the pre-planned 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.
- **Abnormal laboratory results:** Abnormal laboratory results are not AEs unless they are clinically significant. For example, a clinically significant laboratory result is one that

requires treatment (for example a blood transfusion for low hemoglobin) or requires a change in study drug (eg, lowering the dose or withholding study drug while the laboratory finding resolves or stabilizes).

Serious Adverse Event

Note: 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.

A serious adverse event (experience) (SAE) or reaction is any untoward medical occurrence that at any dose:

- Results in death (ie, the AE actually causes or leads to death)
- Is life-threatening (with regards to determining if an AE is serious, "life-threatening" is defined as an AE in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. If either the Investigator or the Sponsor believes that an AE meets the definition of life-threatening, it will be considered life-threatening.)
- Requires in-subject hospitalization > 24 hours or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (ie, the AE results in substantial disruption of the subject's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Is an important medical event that may not result in death, be immediately life-threatening or require hospitalization, but may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject or subject and may require intervention to prevent one of the other outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsion that do not result in hospitalization; or development of drug dependency or drug abuse

Given that the Investigator's perspective may be informed by having actually observed the event, and the Sponsor is likely to have broader knowledge of the drug and its effects to inform its evaluation of the significance of the event, if either the Sponsor or the Investigator believes that the event is serious, the event will be considered serious.

Suspected Adverse Reaction

The FDA has published a guidance on the reporting of SAEs. This document directs Sponsors to consider more carefully the AEs that are reported in an expedited (urgent) fashion to the FDA. Key elements of this guidance are outlined below:

The guidance defines any AE for which there is a "reasonable possibility" that the drug caused the AE as a Suspected Adverse Reaction.

"Reasonable Possibility", for the purposes of safety reporting, means there is evidence to suggest a causal relationship between the drug and the AE. Examples of evidence that would suggest a causal relationship between the drug and the AE are:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (eg, angioedema, blood dyscrasias, rhabdomyolysis, hepatic injury, anaphylaxis, and Stevens - Johnson syndrome).
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (eg, include tendon rupture or heart valve lesions in young adults, or intussusception in healthy infants). If the event occurs in association with other factors strongly suggesting causation (eg, strong temporal association, event recurs on rechallenge), a single case may be sufficiently persuasive; but often, more than one occurrence (from one or multiple studies) would be needed before the Sponsor could make a determination of whether the drug caused the event.
- An aggregate analysis of specific events that can be anticipated to occur in the study population independent of drug exposure. Such events include known consequences of the underlying disease or condition under investigation (eg, symptoms or disease progression), or events unlikely to be related to the underlying disease or condition under investigation, but commonly occur in the study population independent of drug therapy (eg, cardiovascular events in an elderly population). An aggregate analysis (across studies) will identify those events that occur more frequently in the drug treatment group than in a concurrent or historical control group.

This definition of "suspected adverse reaction" and the application of the "reasonable possibility" causality standard is considered to be consistent with the concepts and discussion about causality in the ICH E2A guidance (FDA Guidance for Industry 1995).

Severity

Definitions found in the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 or higher will be used for grading the severity (intensity) of nonhematologic AEs. The CTCAE v4.03 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE v4.03 or higher, 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

The grading scale for hematologic toxicity in subjects with CLL is provided in Appendix E.

Causality

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 F for more detail on assessing causality.

Unexpected Adverse Events

An "unexpected" AE is an AE that is not listed in the Investigator Brochure for acalabrutinib, the approved label for ibrutinib, or is not listed at the specificity or severity that has been observed. For example, hepatic necrosis would be "unexpected" (by virtue of greater severity) if the Investigator Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be "unexpected" (by virtue of greater specificity) if the Investigator Brochure/package insert listed only cerebral vascular accidents.

"Unexpected" also refers to AEs that are mentioned in the Investigator Brochure as occurring with a class of drugs or as anticipated from the pharmacologic properties of the drug, but are not specifically mentioned as occurring with the study drug under investigation.

7.2.2 Documenting and Reporting of Adverse and Serious Adverse Events by Investigators

The Investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, as outlined in the prior sections, are recorded on the CRF. All SAEs also must be reported using the SAE report form (see "Expedited Reporting Requirements for Serious Adverse Events" later in this section).

7.2.2.1 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 adverse events will be reported until 30 days after the last dose of study drug or the start of new anticancer therapy (whichever comes first). After this period, investigators should report serious adverse events or other adverse events 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 until the subject is lost to follow up or withdraws consent. Resolution/stable means the subject has returned to baseline state of health or the Investigator does not expect any further improvement or worsening of the event.

7.2.2.2 Assessment of Adverse Events

Investigators will assess the occurrence of AEs and SAEs at all subject evaluation time points during the study. All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, clinically significant laboratory test (ie, requiring change in study drug dose or discontinuation of study drug or any other medical intervention), or other means will be recorded in the subject's medical record and on the AE CRF and, when applicable, on an SAE/Product Complaint form.

Each recorded AE or SAE will be described by its diagnostic term, duration (ie, start and end dates), severity, regulatory seriousness criteria (if applicable), suspected relationship to study drug, and any actions taken.

7.2.2.3 Adverse Events of Special Interest

The following events are adverse events of special interest (AESIs) and must be reported to the sponsor expeditiously (see Section 7.2.2.7 for reporting instructions), irrespective of regulatory seriousness criteria or causality:

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

7.2.2.4 Second Primary Malignancies

Adverse events (AEs) for malignant tumors reported during a study should generally be assessed as serious AEs (SAEs). If no other seriousness criteria apply, the "Important Medical Event" criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a nonserious AE. For example, if the tumor is included as medical history and progression occurs during the study but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as nonserious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

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

7.2.2.5 Pregnancy

The investigator should report all pregnancies and pregnancies of the partners of subjects within 24 hours of notification using the Pregnancy Report Form. This form should be faxed or emailed to *the AstraZeneca Representative*. Any pregnancy-associated SAE must be reported

using the SAE report form, according to the usual timeline and direction for SAE reporting as described below.

Any uncomplicated pregnancy that occurs in a study subject or a partner of a treated subject during this study will be reported for tracking purposes only, if agreed to by the subject or the partner of the subject in this study. All pregnancies and partner pregnancies that are identified during or after this study, 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 or 90 days after the last dose of ibrutinib (whichever is longer), will be followed to conclusion, and the outcome reported, as long as the subject or partner has consented to participate in follow-up.

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

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

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

7.2.2.6 Overdose Instructions

In the event of ingestion of more than the recommended dosage per protocol, additional clinical monitoring is recommended by the sponsor. For any subject experiencing an acalabrutinib *or ibrutinib* 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 *or ibrutinib* 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.

7.2.2.7 Expedited Reporting Requirements for Serious Adverse Events*/Adverse Events of Special Interest*

All SAEs*/AESIs* must be reported within 24 hours of discovery. All initial SAE*/AESIs* reports and follow-up information will be reported using the protocol-specific electronic data capture system. If electronic SAE*/AESIs* reporting is not available, paper SAE*/AESIs* report forms must be *sent* to *the AstraZeneca Representative*, or designee. *The AstraZeneca Representative* may request follow-up and other additional information from the investigator (eg, hospital admission/discharge notes and laboratory results).

Whenever possible, SAEs*/AESIs* should be reported by diagnosis term not as a constellation of symptoms. All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself. The primary cause of death on the autopsy report should be the term reported. Autopsy and postmortem reports must be forwarded to *the AstraZeneca Representative*, or designee, as outlined above.

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

An SAE*/AESIs* may qualify for mandatory expedited reporting to regulatory authorities if the SAE*/AESIs* is attributable to the study drug and is not listed in the current Investigator Brochure (ie, an unexpected event). In this case, Acerta Pharma will forward a formal notification describing the suspected unexpected serious adverse reaction (SUSAR) to all investigators. Each investigator must then notify his or her IRB/IEC of the SUSAR.

7.2.2.8 Other Safety Issues Requiring Expedited Reporting

For studies being conducted in Europe, expedited reporting is required for safety issues that might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. For a detailed description of safety issues that may qualify for expedited reporting please refer to the European Commission guidance titled, “Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use – April 2006” available at http://ec.europa.eu/health/files/eudralex/vol-10/21_susar_rev2_2006_04_11_en.pdf.

7.2.2.9 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. Refer to Appendix J for further instruction on cases of increases in liver biochemistry and evaluation of Hy's law.

7.2.3 Reporting of Serious Adverse Events by Sponsor

Regulatory Authorities, IRBs/IECs, and Investigators will be notified of SAEs in accordance with applicable requirements (eg, GCP, ICH guidelines, national regulations, and local requirements). For the purpose of this protocol, Acerta Pharma considers acalabrutinib and ibrutinib as investigational agents and will follow applicable guidelines for reporting SAEs for both drugs.

8 WITHDRAWAL OF SUBJECT FROM TREATMENT OR ASSESSMENT

8.1 WITHDRAWAL OF SUBJECTS FROM STUDY TREATMENT

Subjects may be withdrawn from study treatment for the following reasons:

- Any subject who has objective evidence of disease progression while receiving protocol-required study drug should be withdrawn from the study treatment. If there is uncertainty regarding whether there is disease progression, the subject may continue study treatment and remain under close observation (eg, evaluated at 2- to 4-week intervals) pending IRC confirmation of disease progression. In particular, transient worsening of disease during temporary interruption of study therapy (eg, for drug-related toxicity, surgery, or intercurrent illness) may not indicate disease progression. In such circumstances, and if medically appropriate, subjects may resume therapy and relevant clinical, laboratory, and/or radiologic assessments should be done to document whether tumor control can be maintained or whether actual disease progression has occurred.
- Toxicity as defined in dose discontinuation sections of the protocol
- Withdrawal from treatment by subject including withdrawal of informed consent
- Drug hold > 28 days
- Second primary malignancy necessitating systemic treatment
- Pregnancy in a subject
- Investigator decision
- Requires prohibited treatment
- Study terminated by sponsor

8.2 REASONS FOR STUDY EXIT

Reasons for study exit include:

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

In case a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation. The measures taken to follow up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal *and scope of withdrawal (e.g., complete or only from treatment and/or protocol assessments)* must be documented in the CRF and in the source documents. Subjects who withdraw consent should still be encouraged to complete the safety follow-up assessments before withdrawing consent, but these assessments cannot be mandated once consent is withdrawn. *In cases of partial withdrawal of consent, subjects should be encouraged to allow future contact for survival follow-up.*

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

9 STATISTICAL METHODS

9.1 GENERAL CONSIDERATIONS

The statistical and analytical plans presented below summarize the more complete plans to be detailed in the statistical analysis plan (SAP). A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters a principal feature of the protocol. The SAP will be finalized before database lock. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

Independent Review Committee

The IRC will be chaired by a physician with expertise in CLL and will conduct response evaluations in accordance with the IRC charter.

Data Monitoring Committee

A DMC, chaired by a physician with expertise in CLL, will monitor the safety of the subjects in this study. An early safety analysis will be performed after approximately 50 subjects have been treated for approximately 8 weeks. This analysis will focus on deaths, treatment discontinuations, SAEs, and Grade 3/4 AEs as well as special events of interest. The Medical

Monitor will review, in a blinded fashion, this information on an ongoing basis until this early safety analysis is conducted. Detailed information on the role of the DMC and frequency of meetings, which occur at least every 6 months, will be provided in the DMC charter separate from this protocol.

9.2 RANDOMIZATION

This study will use an IWRS for randomization. Subjects will be randomized in a 1:1 ratio to receive either acalabrutinib or ibrutinib with the following stratification factors:

- Presence of 17p del
- ECOG performance status (ECOG = 2 versus ECOG ≤ 1)
- Number of prior therapies (1-3 versus ≥ 4)

The treatment assignment for any individual study subject will not be known to study and site personnel or the subject before subject randomization into the study.

9.3 DETERMINATION OF SAMPLE SIZE

A recently completed trial that studied PFS in CLL (Byrd 2014) showed that ibrutinib (the reference/comparator drug in Protocol ACE-CL-006) was superior to ofatumumab, a drug approved for the treatment of CLL in patients with previously treated CLL. Superiority in that study was shown in the overall study population (HR=0.21) as well as in patients with 17p del (HR=0.25) or 11q del (HR=0.14).

Protocol ACE-CL-006 is designed to have 80% power to show that the upper bound of a 2-sided 95% CI for PFS is < 1.429 (the NI bound).

With randomization in a 1:1 ratio, the trial will require approximately 250 events if acalabrutinib and ibrutinib are truly equally effective. Assuming an enrollment period of about CCI and a follow-up period of approximately CCI after the last subject enters the study, the estimated sample size is 500 subjects (250 per arm).

9.4 ANALYSIS POPULATIONS

Intent-to-Treat (ITT) Population

The ITT population will be defined as all subjects randomized.

All efficacy analysis will be performed in the ITT population and will be analyzed as randomized. In addition, the ITT population will be used to summarize demographics, and baseline and disease characteristics.

Safety Population

The safety population includes all subjects who received at least one dose of study drug. The safety population will be the analysis population for the safety analyses. Subjects will be analyzed as treated.

CCI [redacted]

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CCI [redacted]

CCI [redacted]

9.5 HANDLING OF MISSING VALUES/CENSORING/DISCONTINUATIONS

Missing or partial start and end dates for AEs and concomitant medications will be imputed according to prespecified, conservative imputation rules. The SAP will describe the details for handling missing data.

9.6 EFFICACY ANALYSES

9.6.1 Primary Endpoint and Methods

The primary efficacy endpoint is PFS, which is defined as the time from the date of randomization until disease progression (assessed by the IRC per IWCLL 2008 criteria) or death from any cause, whichever occurs first. The primary analysis is event-based and will be conducted after enrollment is completed and approximately 250 *IRC-assessed* events have occurred.

The primary analysis for this study will be conducted to assess whether acalabrutinib is non-inferior to ibrutinib with respect to PFS based on comparison of the upper bound of the 95% CI of HR to the prespecified NI margin of 1.429. The two-sided 95% CI for the HR of acalabrutinib versus ibrutinib will be estimated using a stratified Cox proportional hazard model.

Additional sensitivity and subgroup analyses may be conducted and will be described in SAP.

9.6.2 Secondary Endpoints and Methods

If acalabrutinib is shown non-inferior to ibrutinib, the secondary endpoints will be tested in manner that maintains the Type I error rate at ≤ 5%. The SAP will describe the method*ology* to be used *for multiplicity adjustment*.

Grade ≥ 3 Infections, Richter's Transformation, and Atrial Fibrillation

The incidences of treatment-emergent Grade ≥ 3 infections, Richter's transformation, and atrial fibrillation will be summarized and compared between the 2 treatment arms using 2-sided Cochran-Mantel-Haenszel tests adjusted for the randomization strata.

Richter's transformation will be assessed by central pathology. Incidence of Grade ≥ 3 infections and atrial fibrillation will be collected as described for all AEs (Section 7.2.2).

Overall Survival

Differences between the treatment arms in OS will be assessed using Kaplan-Meier methods and a stratified log-rank test. Medians, ranges, hazard ratios and corresponding 95% CIs will be presented. The OS HR and its 95% CI will be presented using a stratified Cox regression model.

9.6.3 Exploratory Endpoints

CCI [redacted]

CCI [redacted]

Other Exploratory Endpoints

CCI [redacted]

CCI [redacted]

9.7 SAFETY ANALYSES

Safety data will be summarized for the safety population. The baseline value for safety analysis is defined as the value collected at the time closest to and before the start of study drug administration.

Adverse Events

AEs will be graded by the investigator according the National Cancer Institute (NCI) CTCAE v4.03 or higher for non-hematologic AEs. Hematologic toxicity will be assessed by the grading scale for hematologic toxicity in CLL studies in the IWCLL 2008 guidelines. Each AE verbatim term will be coded to a system organ class and a preferred term using the Medical Dictionary for Regulatory Activities (MedDRA).

Treatment-emergent Adverse Events

All TEAEs will be summarized by treatment arm as treated. In addition, AE incidence rates will also be summarized by severity and relationship to study drug.

Grade 3 or Grade 4 TEAEs; TEAEs leading to permanent study drug treatment discontinuation; TEAEs leading to dose reduction; serious TEAEs; TEAEs of special interest and TEAEs resulting in death will be summarized by treatment arm as treated.

Clinical Laboratory Tests

Data Summary Methods:

For gradable parameters, a summary of worst post baseline toxicity grade will be provided in the treatment-emergent period and worst toxicity grade (any grade and Grade 3/4). The difference between groups in percentages will be displayed.

Liver function abnormality by Hy's law and frequencies of abnormal treatment emergent uric acid will be summarized.

Analysis of Lymphocytosis:

For all subjects with baseline and any post-baseline ALC measurements, ALC at peak summary will be provided by treatment arm. *Median percentage change in ALC from baseline with its 95% CI will also be displayed graphically over time.*

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

ECOG Performance Status

ECOG performance status will be collected as scheduled in Appendix A. ECOG performance status grade ranges from 0 to 5. Descriptive statistics will be provided for each visit over time.

Vital Signs and Weight

Body temperature, heart rate (beats/min), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), respiratory rate (breaths/min), and weight will be collected as scheduled in Appendix A. For each parameter, descriptive statistics will be provided over time.

10 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

10.1 REGULATORY AND ETHICAL COMPLIANCE

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

10.2 INSTITUTIONAL REVIEW BOARD (IRB) AND INDEPENDENT ETHICS COMMITTEE (IEC) APPROVAL

The investigator will submit this protocol, the informed consent, Investigator Brochure, and any other relevant supporting information (eg, all advertising materials) to the appropriate IRB/IEC for review and approval before study initiation. A signed protocol approval page; a letter confirming IRB/IEC approval of the protocol and informed consent; and a statement that the IRB/IEC is organized and operates according to GCP and the applicable laws and regulations; **must** be forwarded to Acerta Pharma **before** screening subjects for the study. Additionally, sites must forward a signed FDA 1572 form (Investigator Obligation Form) or local equivalent 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.

10.3 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), **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 the Code of Federal Regulations § 21CFR Part 50, and other applicable national and local regulations governing informed consent. Each subject must provide a signed and dated informed consent before enrollment into this study. In the case of a subject who is incapable of providing informed consent, the investigator (or designee) must obtain a signed and dated informed consent form from the subject's legal guardian. Signed consent forms must remain in each subject's study file and be available for verification by study monitors at any time.

In accordance to individual local and national 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.

10.4 QUALITY CONTROL AND QUALITY ASSURANCE

Sponsor shall implement and maintain quality control and quality assurance procedures to ensure that the study is conducted and data are generated, documented and reported in compliance with the protocol, GCP, and applicable regulatory requirements. This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 2008) and all revisions thereof, and in accordance with FDA regulations (21 CFR Parts 11, 50, 54, 56, and 312, Subpart D – Responsibilities of Sponsors and Investigators) and with the ICH guidelines on GCP (ICH E6).

10.5 STUDY FILES AND RECORD RETENTION

The investigator and other appropriate study staff are responsible for maintaining all documentation relevant to the study. Mandatory documentation includes copies of study protocols and amendments, each FDA Form 1572, IRB/IEC approval letters, signed ICFs, drug accountability records, SAE forms transmitted to Acerta Pharma, subject files (source documentation) that substantiate entries in CRFs, 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. Local regulations may require a longer period for record retention; said local regulations will supersede this protocol. The investigator must notify Acerta Pharma and obtain

written approval from Acerta Pharma before destroying any clinical study records at any time. Acerta Pharma will inform the investigator of the date that study records may be destroyed or return to Acerta Pharma.

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

10.6 CASE REPORT FORMS AND RECORD MAINTENANCE

Authorized study site personnel (see Section 10.9) will complete CRFs designed for this study according to the completion guidelines that will be provided as part of the clinical database. The investigator will ensure that the CRFs are accurate, complete, legible, and completed promptly. Refer to Section 10.5 for record retention requirements.

10.7 INVESTIGATIONAL STUDY DRUG ACCOUNTABILITY

Acalabrutinib capsules must be kept in a locked limited 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.

10.8 STUDY MONITORING/AUDIT REQUIREMENTS

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

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

10.9 INVESTIGATOR RESPONSIBILITIES

A complete list of Investigator responsibilities are outlined in the clinical trial research agreement and the Statement of Investigator FDA Form 1572, both of which are signed by the Investigator before commencement of the study. 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 IND Safety Reports/ SUSAR Reports are submitted promptly to the IRB/IEC.
12. All SAEs are reported to *the AstraZeneca Representative* within 24 hours of knowledge and to the IRB//IEC per their requirements.

10.10 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.

10.11 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.

10.12 PUBLICATION OF STUDY RESULTS

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

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12 APPENDICES

Appendix A: Schedule of Assessments

			Treatment Phase[a]											
Study Weeks		**Screening Phase**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Q4W starting Wk12**	**≥25 Q12W**	***Post Treatment Phase[i]*/ Response Evaluation[b] Q12W/ Q24W**	**ET/SFU visit[c]**	**Post-disease Progression Phase[i] Q12W**
Study Windows		-28 days	± 3 days										± 7 days	+7 days	± 7 days
IP Dispensation			*x*			*x*				*x*	*x*	*x*			
Study Drug Administration															
ARM A	Acalabrutinib 100 mg BID PO		Continuous Daily Dosing												
Arm B	Ibrutinib 420 mg QD PO		Continuous Daily Dosing												
Procedures															
Informed consent		x													
Confirm eligibility & randomize		x													
Medical history		x													
ECOG status		x								x	x	x			
Physical Exam		x	x	x	x	x	x	x	x	x	x	x	x	x	
Vital signs		x	x	x	x	x	x	x	x	x	x	x		x	
ECG		x												x	
[redacted]															
[redacted]															
Concomitant medications		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	
Pregnancy test		x												x	
Hepatitis serologies[f]		x													
HBV PCR[g]							x				*x*	*x*			*x*
Cytogenetics, FISH panel & molecular markers		x													
Hematology		x	x	x	x	x	x	x	x	x	x	x	ANC, ALC, PLT, Hgb (within 7 days of CT)	x	

Serum chemistry	x	x			x				x	x	x		x	
Serum immunoglobulins, β2-microglobulin, T/B/NK counts	x									x	x			
CCI														
CT scans	x[h]											x		
Overall response assessment												x		
Bone marrow biopsy and aspirate	x											CCI		
Survival status and new anticancer therapy														x

Abbreviations: ALC = absolute lymphocyte count; ANC = absolute neutrophil count; anti-HBc = hepatitis B core antibody; CCI CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ET = early termination; FISH = fluorescence in situ hybridization; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; Hgb = hemoglobin level; IV = intravenous; IVIG = intravenous immunoglobulins; CCI PLT = platelet count; PO = oral; CCI Q12W = every 12 weeks; Q24W = every 24 weeks; QM = every month; SFU = safety follow-up.

a. Treatment Period begins with randomization and ends with last dose of study drug. Subjects will take study drug until disease progression or unacceptable toxicity. Subjects will have weekly visits during the first 8 weeks then will have visits every 4 weeks (ie, after Week 8 the next scheduled visit would be at Week 12) through 24 weeks. Thereafter, visits will be every 12 weeks (ie, after Week 24 the next scheduled visit would be at Week 36).

b. Response evaluations will be done every 12 weeks from Week 1 Day 1 through Week 100, and then every 24 weeks *until 5 years on study and then yearly* thereafter until disease progression regardless of whether or not a subject has discontinued study drug. Hematology results must be done within 7 days of CT scans. CCI

c. An early termination visit will be done for subjects who permanently discontinue study drug early for any reason. The safety follow up visit is conducted 30 (+ 7) days after the last dose of *study treatment regardless of whether the* subject receives a new anticancer therapy *or demonstrates disease progression* within this timeframe. *The ET visit should be performed within 7 days of the last dose of all study drugs, if possible, and is not required for subjects who discontinue from the study within 10 days of a scheduled study visit or if the ET visit would be performed within 14 days of the SFU visit.*

d. CCI

e. CCI

f. Hepatitis serology must include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (anti-HBc), and hepatitis C (HCV) antibody. Subjects who are receiving prophylactic intravenous immunoglobulins (IVIG) and have positive HBsAg or anti-HBc must have negative hepatitis B DNA to be eligible. In addition, any subjects testing positive for any hepatitis serology, must have polymerase chain reaction (PCR) testing (see exclusion criterion #15).

g. Subjects who are anti-HBc positive should be *monitored every 3 months with a quantitative PCR test for HBV DNA. Monitoring should continue 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.

h. Subjects who have standard of care CT/MRI results may use these results in lieu of the Screening CT/MRI required for this study, provided the CT/MRI was done within 28 days of first dose and was acquired in accordance with the guidelines outlined in Section 7.1 CT Scans.

i. Subjects who discontinue study drug for reasons other than disease progression will enter the Post Treatment Phase and will have Response Evaluation assessed every 12 weeks (±7 days) through Week 100, and then every 24 weeks until 5 years on study and then yearly thereafter until disease progression.

j. Post-disease Progression Phase will begin once a subject has progressive disease.

Appendix B: Performance Status Scores

Status	Eastern Cooperative Oncology Group (ECOG) Performance Status*
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, 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 selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead.

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

Available at: http://www.ecog.org/general/perf_stat.html. Accessed March 2015.

Appendix C: Examples of Coadministered Drugs That Need Additional Consideration

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

Strong Inhibitors of CYP3A	***Moderate Inhibitors of CYP3A***
boceprevir	*aprepitant*
clarithromycin[a]	*cimetidine*
cobicistat[a]	*ciprofloxacin*
conivaptan[a]	*clotrimazole*
danoprevir and ritonavir[b]	*crizotinib*
diltiazem[a]	*cyclosporine*
elvitegravir and ritonavir[b]	*dronedarone*[a]
grapefruit juice	*erythromycin*
idelalisib	*fluconazole*
indinavir and ritonavir[b]	*fluvoxamine*
itraconazole[a]	*imatinib*
ketoconazole	*tofisopam*
lopinavir and ritonavir[a,b]	*verapamil*[a]
nefazodone	
nelfinavir[a]	
paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)[b]	
posaconazole	
ritonavir[a, b]	
saquinavir and ritonavir[a, b]	
telaprevir[a]	
tipranavir and ritonavir[a, b]	
troleandomycin	
voriconazole	

a. *Inhibitor of P-glycoprotein.*

b. *Ritonavir is usually given in combination with other anti-HIV or anti-HCV drugs in clinical practice. Caution should be used when extrapolating the observed effect of ritonavir alone to the effect of combination regimens on CYP3A activities.*

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

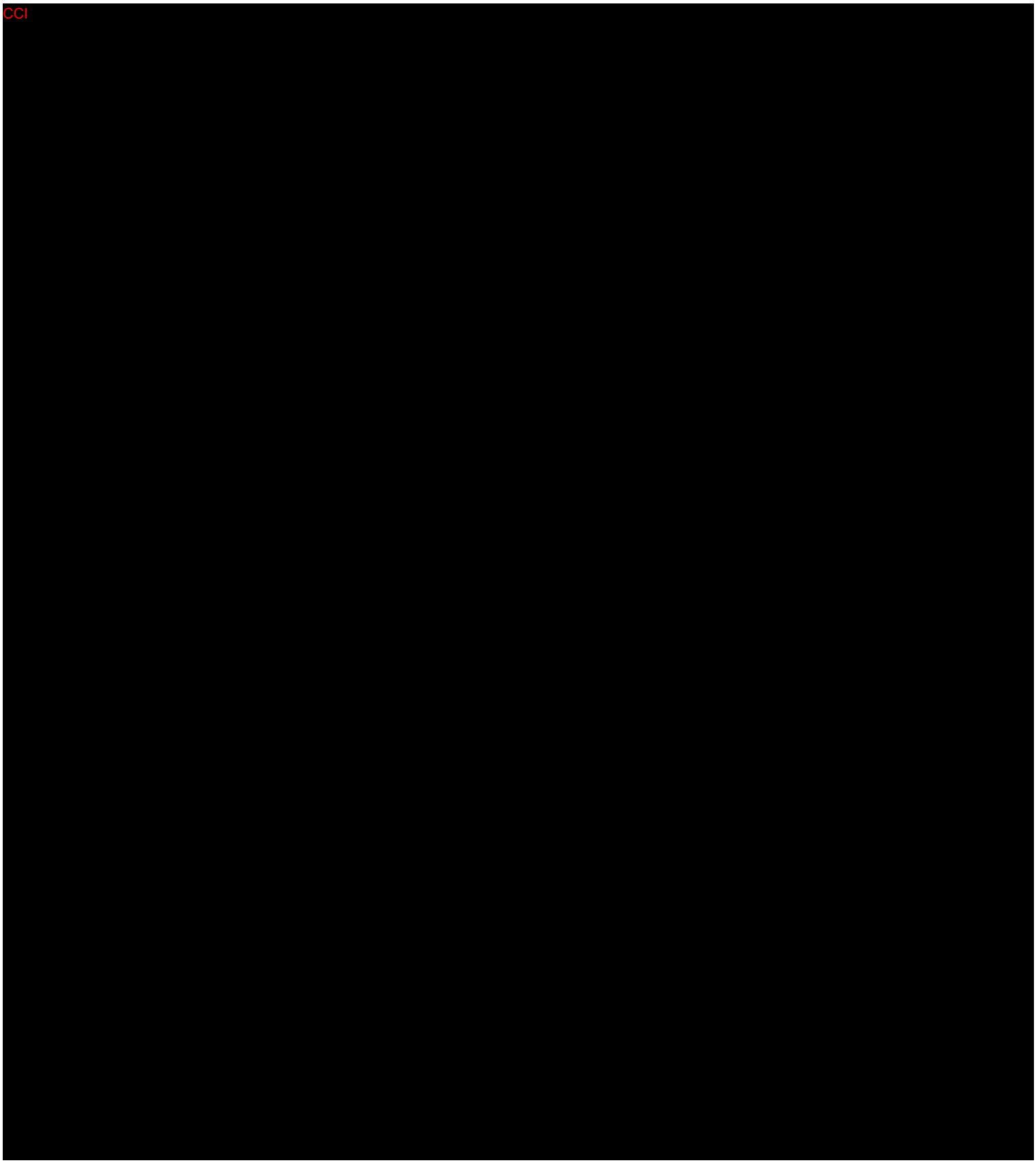
a. *The effect of St. John's wort varies widely and is preparation-dependent.*

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

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

Appendix D: CCI

CCI



Appendix E: Hematologic Adverse Event Grading Scheme (Hallek 2008)

An evaluation of the hematologic toxicity in subjects with advanced CLL must consider the high frequency of marrow involvement and previous exposure to chemotherapy with consequent medullary compromise at the initiation of therapy. The standard hematologic grading system for solid tumors cannot, therefore, be directly applied. A substantial proportion of subjects would be considered to have Grade 2 to 4 hematologic toxicity before any therapy is given. Therefore, the following modified schema will be used to quantitate hematologic deterioration in subjects with CLL.

Hematologic Grading Scheme

Grade[1]	Decrease in platelets[2] or Hb[3] (nadir) from pretreatment value	Absolute neutrophil count/μL[4] (nadir)
0	No change to 10%	≥ 2000
1	11%-24%	≥ 1500 and < 2000
2	25%-49%	≥ 1000 and < 1500
3	50%-74%	≥ 500 and < 1000
4	≥ 75%	< 500

1. Grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, fatal. Death occurring as a result of toxicity at any level of decrease from pretreatment will be reported as Grade 5.
2. Platelet counts must be below normal levels for Grades 1 to 4. If, at any level of decrease, the platelet count is < 20 x 10^9/L (20,000/μL), this will be considered Grade 4 toxicity, unless a severe or life-threatening decrease in the initial platelet count (eg, < 20 x 10^9/L [20,000/μL]) was present pretreatment, in which case the patient is not evaluable for toxicity referable to platelet counts.
3. Hemoglobin (Hb) levels must be below normal levels for Grades 1 to 4. Baseline and subsequent Hb determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity, but should be documented.
4. If the ANC reaches < 1 x 10^9/L (1000/μL), it should be judged to be Grade 3 toxicity. Other decreases in the white blood cell count, or in circulating neutrophils, are not to be considered because a decrease in the white blood cell count is a desired therapeutic endpoint. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was < 1 x 10^9/L (1000/μL) before therapy, the patient is not evaluable for toxicity referable to the ANC. The use of growth factors such as granulocyte colony-stimulating factor (G-CSF) is not relevant to the grading of toxicity, but should be documented.

Appendix F: 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

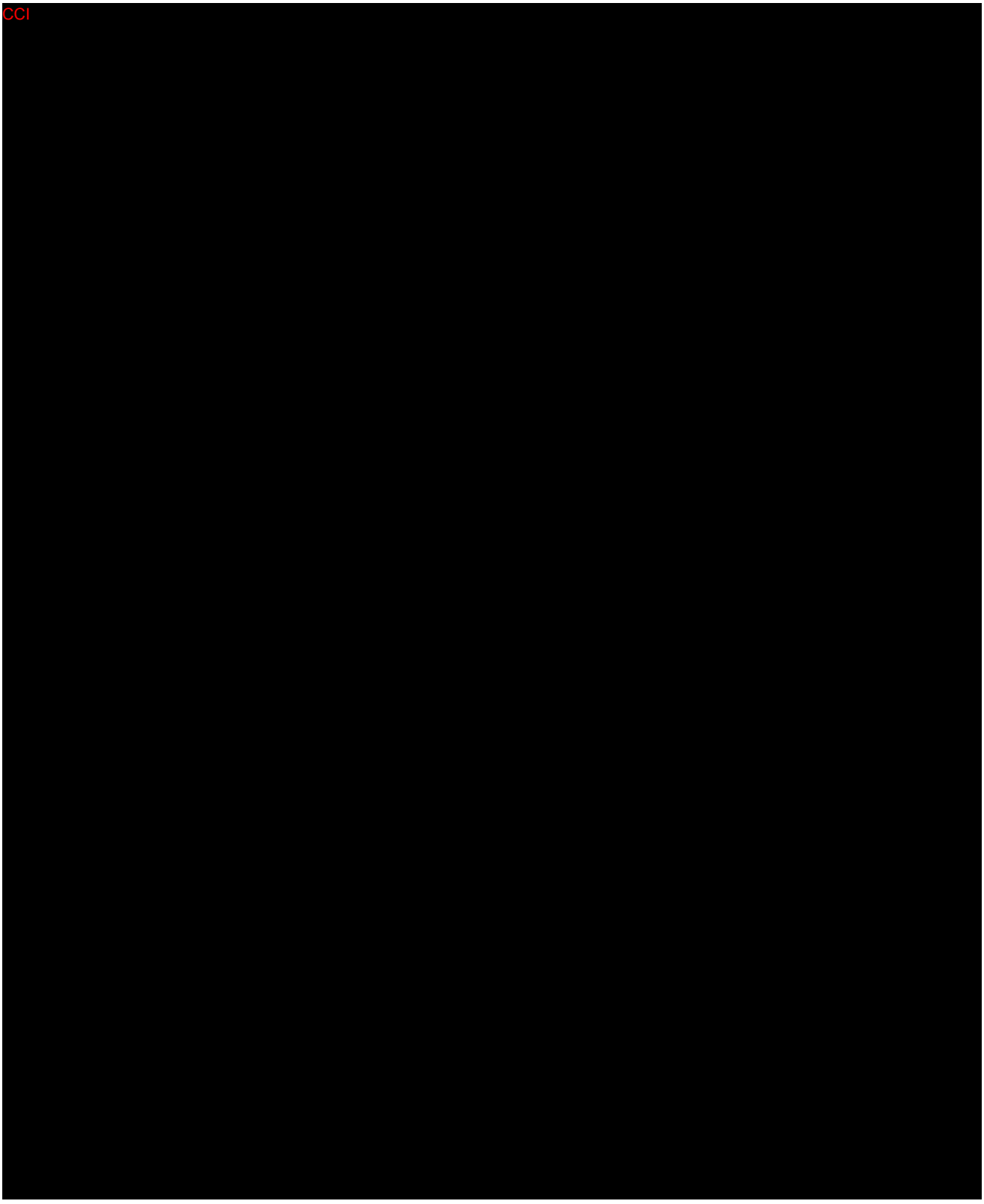
Yes = There is a reasonable possibility that the event may have been caused by study drug.

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 G: CCI

CCI



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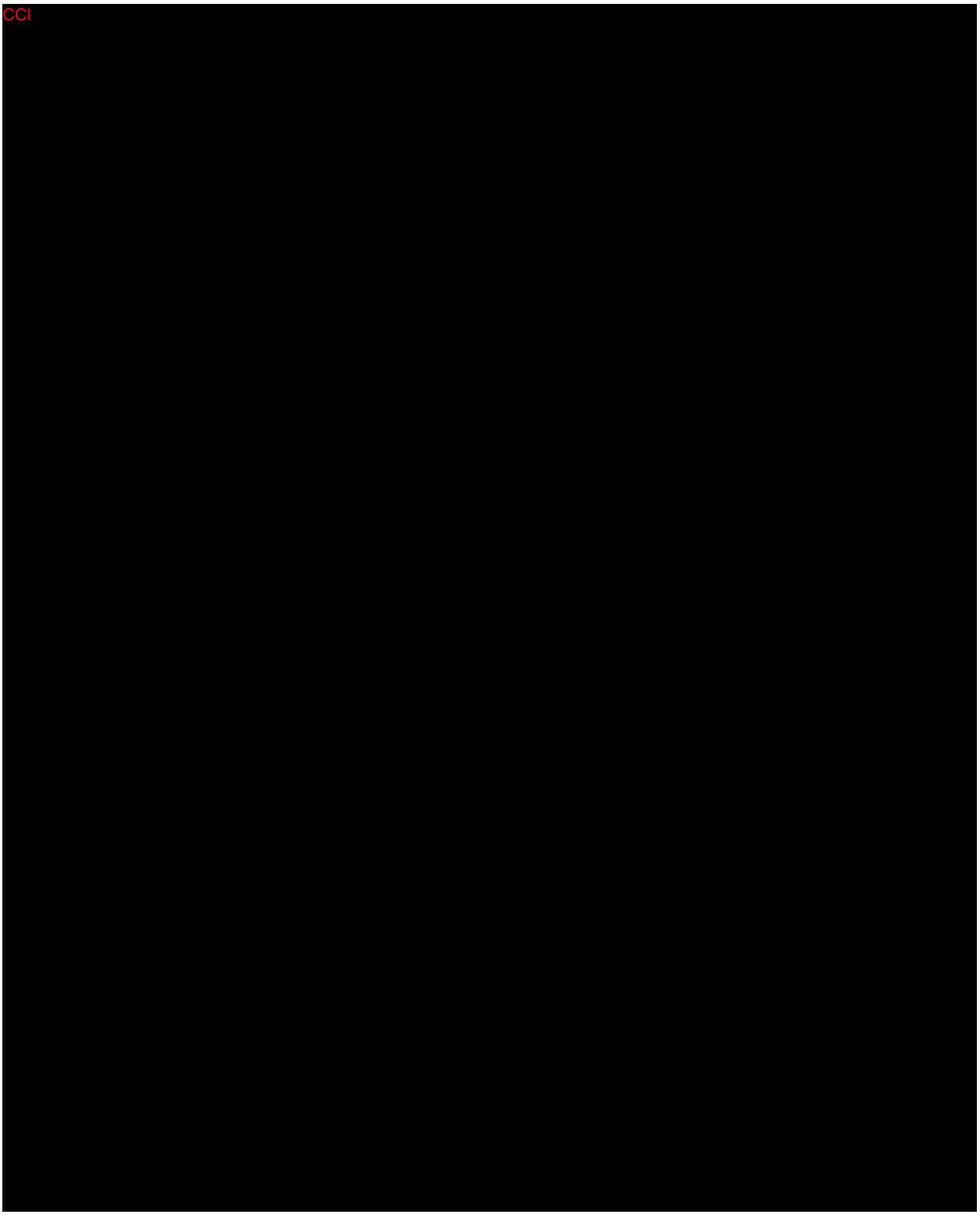
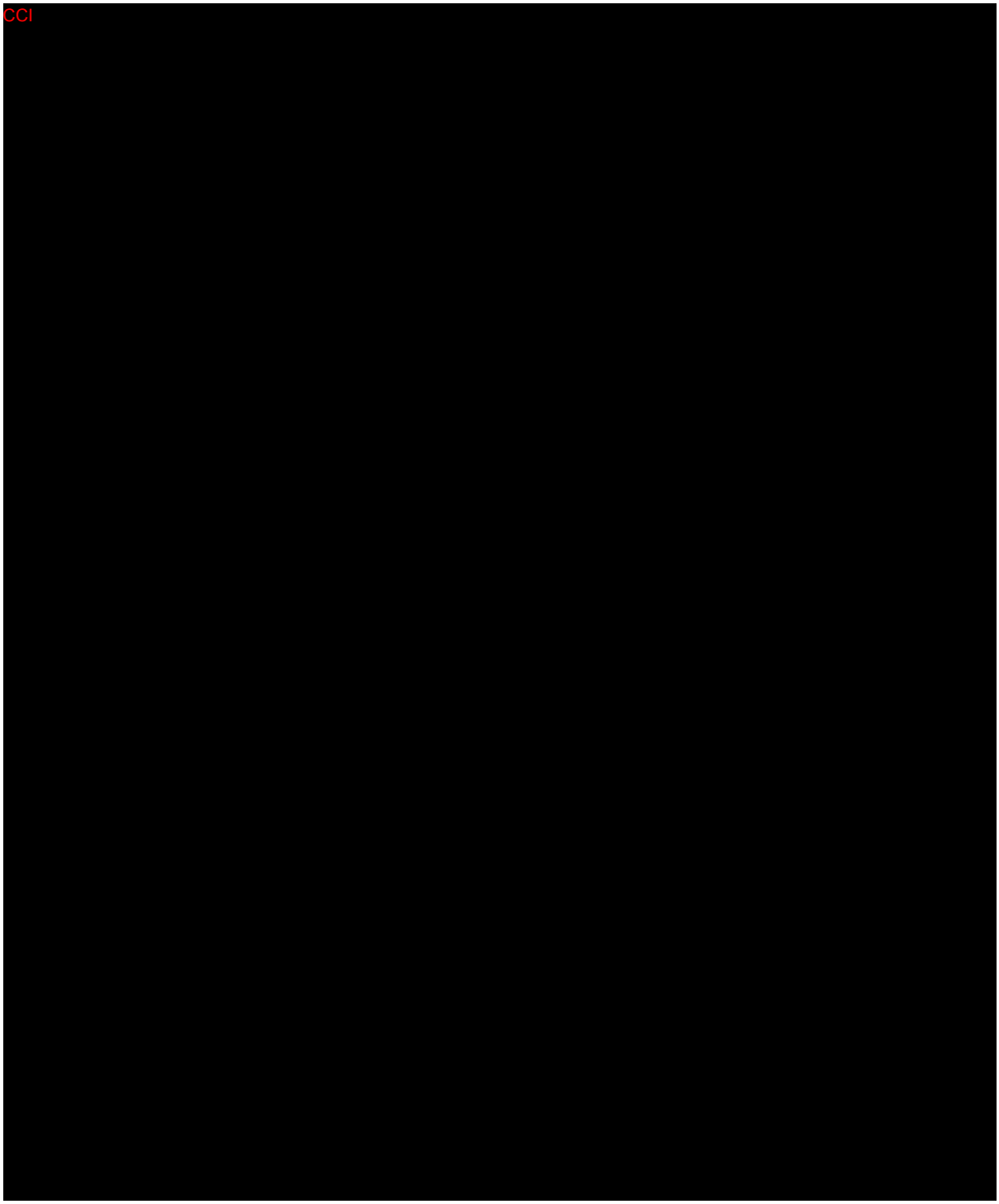


Appendix H: CCI

CCI



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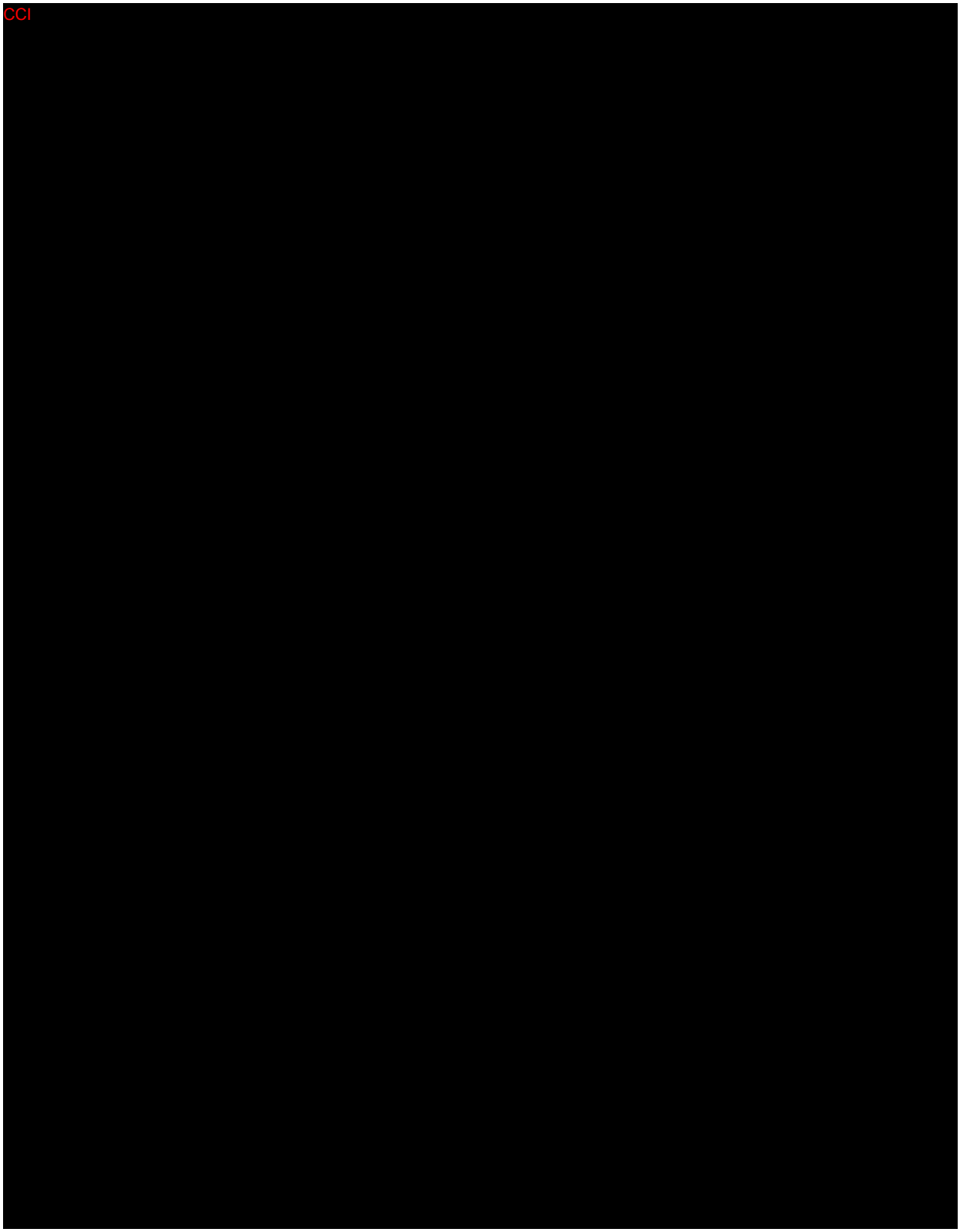
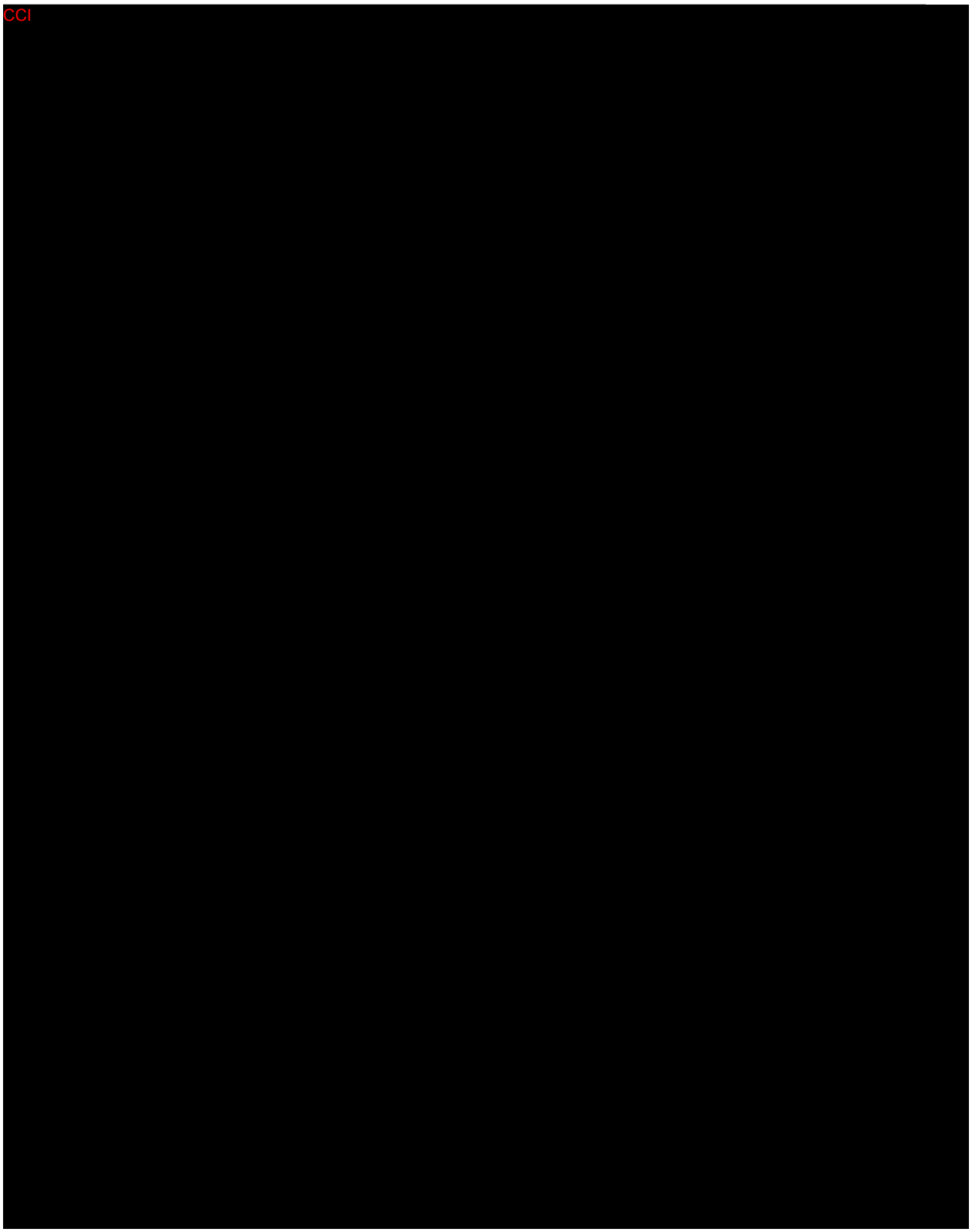


Appendix I: CCI

CCI



Appendix J: 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.

Appendix K: Management of Study Procedures During Pandemic

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

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

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

CONDUCT OF TELEPHONE VISITS

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

ACALABRUTINIB DOSE MODIFICATION RECOMMENDATION FOR COVID-19

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

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

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

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

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

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

Please contact the study medical monitor for further discussion.

COMPARATOR DRUGS OR DRUGS USED IN COMBINATION WITH ACALABRUTINIB:

- *Please refer to guidance from the manufacturer.*

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

Drug-Drug Interaction Guidance for Investigators with Subjects Enrolled in an Acalabrutinib Clinical Study who are COVID-19 Positive:

- *The potential combination with chloroquine or 8-8-OH-chloroquine (8-OH-CHQ) and azithromycin are not predicted to have a pharmacokinetic DDI with acalabrutinib. However, both agents are known to cause cardiovascular risk of QT-prolongation. Therefore, the risk/benefit of initiating 8-OH-CHQ + azithromycin should be discussed with the medical monitor.*
- *Many antivirals and antibiotics are considered strong CYP3A4 inhibitors or inducers and are therefore likely to cause complex DDIs with acalabrutinib. The risk-benefit balance of acalabrutinib use in the setting of COVID-19 treatment should be discussed between the investigator and the medical monitor.*
- *Remdesivir is rapidly metabolized to a pharmacologically active metabolite, GS-443902. Based on published and publicly available data, remdesivir does not appear to inhibit*

CYP isoforms and will likely not interact in a meaningful way with drug transport systems. Remdesivir does not prolong QTc interval.

- *Systemic steroids and acalabrutinib may impair the ability of the body to fight infection; it is best to avoid high-dose systemic steroids while taking acalabrutinib.*
- *The study protocol and investigator brochure should be referenced for other DDI information.*

COVID-19 Specific Data Entry Instructions for Investigational Sites

Adverse Event Recording:

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

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

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

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

Study Treatment Recording:

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

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

- *Related to AE:*
  On the Dose Administration Forms(s), dose change/missed should be indicated with AE as the reason. The dosing stop date must correlate to the AE/SAE start/stop dates.
- *Related to Logistics:*

For subjects who have missed a study treatment due to an inability to travel to the clinic or for some other logistical reason, on the Dose Administration Form(s) dose change/missed should be indicated with Other as the reason, and "Logistic" as Other, Specify.

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

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

Capturing telephone contacts with subjects:

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

1. *If the visit is specified as a phone visit as per protocol, no additional action is required.*
2. *If the visit is listed as on-site but the subject will be contacted by phone, data should be completed as per a normal visit (i.e., using the relevant eCRF pages to capture a phone Visit Date, and any possible assessment that can be obtained remotely should be captured, such as AEs, study drug administration and/or concomitant medications, and any additional safety information). All assessments that cannot be performed should be marked as not done or eCRF inactivated/marked Blank. A protocol deviation should be recorded in the clinic notes prefixed COVID19 detailing the use of a phone visit in place of an onsite visit.*
3. *If the visit requires procedures that cannot be performed via telephone contact (e.g., MRI or CT Scan), this should be discussed with the site monitor because this procedure may impact primary efficacy or safety analyses.*

Acalabrutinib Site-to-Subject Drug Shipment Instructions During Pandemic Containment or in Case of Force Majeure

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

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

- *The sponsor is responsible for delivery of the study drug to the study site. Any shipments made from the site to the subject will be the responsibility of the study site.*
- *The subject is informed about the shipment method, confirms the address for receipt of the drug, and agrees that his or her personal information (i.e., name and address) may be given to a professional carrier.*

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