PROTOCOL

TITLE:	A Randomized, Multicenter, Open-Label, 3 Arm Phase 3 Study of Obinutuzumab in Combination with Chlorambucil, ACP-196 in Combination with Obinutuzumab, and ACP-196 Monotherapy in Subjects with Previously Untreated Chronic Lymphocytic Leukemia
PROTOCOL NUMBER:	ACE-CL-007
STUDY DRUG:	Acalabrutinib (ACP-196)
IND NUMBER:	118717
EUDRACT NUMBER:	2014-005582-73
SPONSOR MEDICAL MONITOR:	PPD Phone: PPD Email:PPD
SPONSOR:	Acerta Pharma, BV PPD 5349 AB Oss The Netherlands
ORIGINAL PROTOCOL:	Version 0.0 – 11 March 2015
AMENDMENTS:	Version 1.0 – 01 April 2015 Version 2.0 – 27 April 2015 Version 3.0 – 16 March 2016 Version 4.0 – 06 March 2017 Version 5.0 – 04 December 2017 Version 6.0 – 17 June 2020

Confidentiality Statement

PROTOCOL APPROVAL

Version 6.0

I have carefully read Protocol ACE-CL-007 entitled "A Randomized, Multicenter, Open-Label, 3 Arm Phase 3 Study of Obinutuzumab in Combination with Chlorambucil, ACP-196 in Combination with Obinutuzumab, and ACP-196 Monotherapy in Subjects with Previously Untreated Chronic Lymphocytic Leukemia". I agree to conduct this study as outlined herein and in compliance with Good Clinical Practice (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 6.0

This protocol is being amended to update clinical trial data and safety information, including Reference Safety Information, based on the current Acalabrutinib Investigator Brochure as well as to clarify hepatitis testing during crossover, to add Rollover and Safety Extension Study text, to add Hy's law information, CCI will no longer be collected, investigator-assessed progressive disease (PD) after crossover will be confirmed by the study Medical Monitor, to clarify several study details, and to correct inconsistencies.

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

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

Summary of Changes for Amendment 6.0

Section(s) Impacted	Rationale
Headers and Footers	Updated to align with Acerta protocol standards
Updated heading numbers throughout protocol	Updated heading numbers to align with new Acerta protocol template
Title page	Updated Medical Monitor and contact information
Study Synopsis	Updated the Synopsis to reflect changes in the protocol.
1.3.1 Chemistry	Updated this section with Calquence approval in CLL and SLL.
1.4.2 Clinical Experience of Acalabrutinib in CLL	Updated based on the current Acalabrutinib Investigator Brochure.
3.4 Exploratory Objectives	CCI
4.1 Treatment Arm A: Obinutuzumab in Combination with Chlorambucil	Added text for Arm A crossover subjects: "After the interim analysis and per Amendment 6.0, at investigator discretion, subjects randomized to Arm A, who have IRC-confirmed progressive disease (PD) (through Amendment 5.0) or investigator-assessed PD (Amendment 6.0) will be eligible to receive crossover treatment with single-agent acalabrutinib at 100 mg BID until disease progression or unacceptable toxicity. However, the investigator-assessed PD must be confirmed by the study Medical Monitor." The rationale for this change is that the IRC primary endpoint has been met. Sponsor review is deemed sufficient.

4.4 Crossover	Added text that screening for eligibility may occur concurrently with the study Medical Monitor as needed. Added text that IRC assessments for confirmation of PD for crossover subjects was required through Amendment 5.0. Added that any new systemic therapy or crossover treatment with acalabrutinib could not be started without investigator-assessed PD confirmed by the study Medical Monitor. The rationale for this change is that the IRC primary endpoint has been met. Sponsor review is deemed sufficient.
4.5 Screening, Treatment, and Follow-up Phases	Added text for the Rollover or Safety Extension Study to ensure treatment continuation, with visit assessments per the rollover or extension protocol and alignment with other acalabrutinib protocols. Revised the following sentence "The Post-disease Progression Phase will begin after IRC-confirmed PD (through Amendment 5.0) or investigator-assessed PD (Amendment 6.0); investigator-assessed PD must be confirmed by the study Medical Monitor." The rationale for this change is that the IRC primary endpoint has been met. Sponsor review is deemed sufficient.
6.3.3.1 Tumor Lysis Syndrome for acalabrutinib	Added this section and text for subjects considered at risk for TLS on acalabrutinib
6.4.1.1 Hemorrhage	Updated based on the current Acalabrutinib Investigator Brochure.
6.4.1.2 Infections	Updated based on the current Acalabrutinib Investigator Brochure.
6.4.1.5 Cytopenias	Updated based on the current Acalabrutinib Investigator Brochure.
6.4.1.6 Second Primary Malignancies	Updated based on the current Acalabrutinib Investigator Brochure.
6.4.1.7 Atrial Fibrillation	Updated based on the current Acalabrutinib Investigator Brochure.
6.4.1.8 Dietary Restrictions	Updated based on the current Acalabrutinib Investigator Brochure.
6.4.4 Reproductive Toxicity	Updated based on the current Acalabrutinib Investigator Brochure.
6.5.2 Guideline for Use of CYP-Inhibiting/Inducing Drugs	Updated based on the current Acalabrutinib Investigator Brochure.
6.5.3 Guideline for Use of Drugs that Affect Gastric pH	Updated based on the current Acalabrutinib Investigator Brochure.
6.5.4 Prohibited Concomitant Medications	Updated based on the current Acalabrutinib Investigator Brochure.
7.1.10 Hepatitis Serologies	Clarified hepatitis testing during the randomized part of the study and the crossover part.
7.1.12 Genetic and Molecular Prognostic Markers	Revised the CCI section to specify that CCI endpoints would not be collected under Amendment 6.0. The rationale for this change is that the exploratory CCI endpoints were met for the study.
7.1.26 Overall Response Evaluations	Revised the sentence to state: "In addition, prior to crossover from Arm A to the crossover arm, a subject may continue treatment and remain under close observation until progression is confirmed by the IRC (through Amendment 5.0) or until progression is assessed by the investigator and confirmed by the study Medical Monitor (Amendment 6.0)."
Added 1 new section within Section 7.2.1 Definitions 7.2.1.3 Adverse Events of Special Interest	This section was added to provide consistency across Acerta's acalabrutinib protocols.

7.2.2.1 Adverse Event Reporting Period	This text has been updated to provide consistency across Acerta's acalabrutinib protocols.
7.2.2.3 Second Primary Malignancies	This section and text have been added to provide safety information and consistency across Acerta's acalabrutinib protocols.
7.2.2.5 Expedited Reporting Requirements for Serious Adverse Events and AESIs	This section was updated to include expedited reporting requirements for AESIs and to provide the source of Reference Safety Information, to provide consistency across Acerta's acalabrutinib protocols.
7.2.2.7 Hy's Law	This section and text have been added to provide safety information and consistency across Acerta's acalabrutinib protocols.
9.9.4 Exploratory Endpoints	CCI [redacted]
9.10.3 AESIs	Revised this section to refer to Section 7.2.1.6 for the definitions of AESIs.
12 Appendices A, B, and C	Added footnote to the Schedule of Assessments tables to clarify that CCI endpoints will not be collected under Amendment 6.0
12 Appendices	Appendix H has been removed: The obinutuzumab and chlorambucil label has been removed from the protocol (previously Appendix H) to ensure the most current labels are accessed by the investigators and sites. The Appendices have been renumbered accordingly.
Appendix F Examples of Coadministered Drugs That Need Additional Consideration	This section was updated to provide safety information and consistency across Acerta's acalabrutinib protocols.
Appendix M Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law	This Appendix has been added to provide detailed safety information, instruction, and consistency regarding Hy's law across Acerta's acalabrutinib protocols.
Appendix N Management of Study Procedures During Pandemic	Appendix N has been added to consolidate guidance for subject safety and ongoing access to medical care and investigational product during the global COVID-19 pandemic.
Entire protocol	Text has been updated throughout the protocol to cite the local prescribing information and SmPCs to ensure the most current labels are accessed by the investigators and sites.

STUDY SYNOPSIS

Study Title:	A Randomized, Multicenter, Open-Label, 3 Arm Phase 3 Study of Obinutuzumab in Combination with Chlorambucil, ACP-196 in Combination with Obinutuzumab, and ACP-196 Monotherapy in Subjects with Previously Untreated Chronic Lymphocytic Leukemia
Protocol Number:	ACE-CL-007
Study Phase:	3
Study Duration:	The study duration will be approximately 4.5 years including enrollment time.
Investigational Product and Reference Therapy:	The investigational product, acalabrutinib (also known as ACP-196), will be supplied as hard gelatin capsules for oral (PO) administration. Commercially available obinutuzumab (GAZYVA / GAZYVARO) and chlorambucil (LEUKERAN®) will be the reference therapy. Obinutuzumab is administered by intravenous (IV) infusion. Chlorambucil is administered orally.
Objectives	**Primary Objective:** • To evaluate the efficacy of obinutuzumab in combination with chlorambucil (Arm A) compared with acalabrutinib in combination with obinutuzumab (Arm B) based on Independent Review Committee (IRC) assessment of progression-free survival (PFS) per 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—in subjects with previously untreated chronic lymphocytic leukemia (CLL). **Secondary Objectives**: • To evaluate the efficacy of obinutuzumab in combination with chlorambucil (Arm A) versus acalabrutinib monotherapy (Arm C) based on IRC assessment of PFS per IWCLL 2008 criteria. • To compare obinutuzumab plus chlorambucil (Arm A) versus acalabrutinib plus obinutuzumab (Arm B) and obinutuzumab plus chlorambucil (Arm A) versus acalabrutinib monotherapy (Arm C) in terms of: • IRC-assessed objective response rate (ORR) per IWCLL 2008 criteria. • Time to next treatment (TTNT) (defined as the time from randomization to institution of non-protocol specified treatment for CLL). • Overall survival (OS).

	Safety Objective: • Incidence of adverse events (AEs) and serious adverse events (SAEs) and changes in laboratory measurements. **Exploratory Objectives:** CCI [redacted]
Study Design:	This randomized, global, multicenter, open-label, 3-arm Phase 3 study will evaluate the efficacy and safety of Arm A, Arm B, and Arm C in subjects with previously untreated CLL. Approximately 510 eligible subjects will be randomized in a 1:1:1 ratio into 3 arms (n=170) to receive either Arm A (obinutuzumab in combination with chlorambucil per the package

	inserts), Arm B (acalabrutinib 100 mg twice per day [BID] in combination with obinutuzumab per the package insert), or Arm C (acalabrutinib 100 mg BID). 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 (e.g., demographic and baseline characteristics) are evenly balanced, and to enhance the validity of statistical comparisons across treatment groups. Subjects will be randomized based on the following stratification factors: • Presence versus absence of 17p deletion mutation (17p del). • Eastern Cooperative Oncology Group (ECOG) Performance Status 0, 1 versus 2. • Geographic region (North America and Western Europe versus Other). 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 the 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(s) discontinuation. Treatment with acalabrutinib may be continued until an unacceptable drug-related toxicity occurs or until disease progression. Dose modification provisions are provided in the study protocol. Note: temporary withholding of acalabrutinib 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. Treatment with obinutuzumab or obinutuzumab/chlorambucil is up to 6 cycles per the obinutuzumab package insert. Assessment for tumor response and progression will be conducted in accordance with the IWCLL 2008 criteria until disease progression. Disease assessments will be done every 12 weeks (± 14 days) with the first on-treatment radiologic assessment occurring on Cycle 4 Day 1, the second on-treatment scan on Cycle 7 Day 1, and so on through Cycle 25, and then every 24 weeks (± 14 days) thereafter for all subjects (including subjects who discontinue from study treatment due to an AE or any reason) until confirmation of disease progression or death, consent withdrawal, or lost to follow up. Subjects from Arm A who have IRC-confirmed disease progression may be eligible to receive single agent acalabrutinib at 100 mg PO BID at investigator discretion. A pre-planned interim analysis was performed and met the primary objective.

	After the interim analysis and per Amendment 6.0, subjects can crossover with either IRC-confirmation (through Amendment 5.0) or investigator-assessed (Amendment 6.0) progressive disease (PD); however, the investigator-assessed PD must be confirmed by the study Medical Monitor An early termination (ET) visit is required for safety assessments for any subjects who permanently discontinue study treatment for any reason (except for death, lost to follow-up or withdrawal of consent), 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 treatment within 10 days of a scheduled study visit or if the ET visit would be performed within 14 days of the safety follow-up (SFU) visit. If the SFU visit is within ± 7 days of a regularly scheduled visit during the Post-treatment Phase, these visits may be combined into a single visit. In addition to the ET visit, a SFU visit should be conducted 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 demonstrated disease progression within this time frame. Per Amendment 6.0, the Post-disease Progression Phase will begin after IRC-confirmed (through Amendment 5.0) or investigator-assessed (Amendment 6.0) progressive disease, if confirmed by the study Medical Monitor. During this phase, subsequent anticancer therapy with start date of therapy, IWCLL indication for treatment initiation, additional malignancy occurrence, and 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. Subjects who are still on treatment at the end of the study (ACE-CL-007) and deriving clinical benefit from acalabrutinib treatment may continue treatment. At the time of the final data cutoff (DCO) and database closure, subjects who remain in this study may be transitioned to a separate rollover study or remain within this study for continued access to study drug. Once all active subjects are eligible to continue to receive acalabrutinib and after database closure, this study will be considered closed. There will be no further data collection other than reporting of SAEs per Section 7.2.2.5. Access within this study will enable continued treatment with visit assessments per standard of care, whereas the separate rollover study will enable treatment continuation with visit assessments and data collection per the rollover study protocol.
Population:	Subjects with previously untreated CLL
Centers:	Approximately 200 global centers in North America, Europe, Australia/New Zealand, and Latin America.

Inclusion Criteria:	1. Men and women: a. ≥ 65 years of age, **OR** b. > 18 and < 65 years of age provided that they meet at least one of the following criteria: i. Creatinine clearance 30 to 69 mL/min using the Cockcroft-Gault equation. ii. A score higher than 6 on the Cumulative Illness Rating Scale-Geriatric (CIRS-G) (Appendix L). 2. ECOG performance status of 0, 1, or 2. 3. Diagnosis of $CD20^+$ 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. 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 (i.e., ≥ 6 cm below the left costal margin), progressive, or symptomatic splenomegaly. c. Massive nodes (i.e., ≥ 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 (e.g., 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 (i.e., ECOG performance status 2; 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. 5. This criterion was removed as of Protocol Amendment 3Meet 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 ≥ 50,000 cells/µL (50 x 10^9/L), or ≥ 30,000 cells/µL (30 x 10^9/L) in subjects with documented bone marrow involvement, and without transfusion support 7 days before assessment. Subjects with transfusion-dependent thrombocytopenia are excluded. c. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 x upper limit of normal (ULN). d. Total bilirubin ≤ 1.5 x ULN. e. Estimated creatinine clearance (i.e., estimated glomerular filtration rate [eGFR] using Cockcroft-Gault) ≥ 30 mL/min. 7. Able to receive all outpatient treatment, all laboratory monitoring, and all radiologic evaluations. 8. 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 18 months after the last dose of obinutuzumab in combination with chlorambucil, whichever is longer. Highly effective forms of contraception are defined in Section 6.4.4. 9. 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 obinutuzumab or chlorambucil, whichever is later. Highly effective forms of contraception are defined in Section 6.4.4. 10. Men must agree to refrain from sperm donation during the study and for 90 days after the last dose of obinutuzumab or chlorambucil, whichever is later.

	11. 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, as defined in International Conference on Harmonisation (ICH) GCP, are not allowed on this protocol (e.g., prisoners or institutionalized subjects).
Exclusion Criteria:	1. Any prior systemic treatment for CLL (note: Prior localized radiotherapy is allowed). 2. Known central nervous system (CNS) lymphoma or leukemia. 3. Known prolymphocytic leukemia or history of, or currently suspected, Richter's syndrome. 4. Missing or incomplete documentation of FISH results reflecting the presence or absence of 17p del and the percentage of cells with the deletion in subject records before randomization. 5. 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). 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 (WBC) lowering are excluded. 7. Major surgery within 4 weeks before first dose of study drug. 8. 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. 9. 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. 10. 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. 11. 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. 12. Known history of infection with human immunodeficiency virus (HIV). 13. Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug. 14. 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. 15. History of stroke or intracranial hemorrhage within 6 months before randomization. 16. History of a bleeding diathesis (e.g., hemophilia, von Willebrand disease). 17. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon) within 7 days of first dose of study drug. 18. Requires treatment with proton-pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). 19. Breast feeding or pregnant. 20. Current life-threatening illness, medical condition, or organ system dysfunction which, in the Investigator's opinion, could compromise the subject's safety or put the study at risk. 21. Concurrent participation in another therapeutic clinical trial. 22. Requires treatment with a strong cytochrome P450 3A (CYP3A) inhibitor/inducer. 23. Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before screening

Primary Endpoint:	The primary endpoint of the study is PFS as assessed by IRC review per IWCLL 2008 criteria. The primary analysis is a comparison of PFS between Arm A and Arm B.
Secondary Endpoints:	Efficacy: The first secondary endpoint is a comparison of IRC-assessed PFS between Arm A and Arm C. Other secondary endpoints are as follows and compare Arm A versus Arm B and Arm A versus Arm C in terms of: • ORR defined as complete remission (CR), complete remission with incomplete bone marrow recovery (CRi), nodular partial remission (nPR), or partial remission (PR) (per IWCLL 2008 criteria). • TTNT (defined as the time from randomization to institution of non-protocol specified treatment for CLL). • OS. Safety: • 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: Acalabrutinib is provided as 100-mg hard gelatin capsules for PO administration. Acalabrutinib 100 mg will be administered BID until disease progression or unacceptable toxicity. For subjects randomized to Arm B (acalabrutinib in combination with obinutuzumab), acalabrutinib administration will begin 28 days before the first dose of obinutuzumab (i.e., acalabrutinib begins on Cycle 1 Day 1, obinutuzumab begins on Cycle 2 Day 1). Obinutuzumab: Commercially available obinutuzumab will be supplied as a liquid concentrate (25 mg/mL) for dilution for IV administration Obinutuzumab must be administered as an IV infusion and premedication is required. Obinutuzumab will be administered for a maximum of 6 cycles. Refer to the obinutuzumab local prescribing information for more details. Chlorambucil: Commercially available chlorambucil will be provided as film-coated tablets (2 mg) for PO administration. In this study, chlorambucil will be administered for a maximum of 6 cycles in combination with obinutuzumab. Refer to chlorambucil local prescribing information for more details.

Concomitant Therapy and Clinical Practice:	**Permitted Concomitant Therapy** Standard supportive care medications are permitted; this includes premedication for obinutuzumab infusion as per the obinutuzumab package insert. Use of hematopoietic growth factors is permitted per the American Society of Clinical Oncology (ASCO) guidelines. For subjects considered at risk for tumor lysis syndrome (TLS), administer appropriate hydration and allopurinol or rasburicase per institutional standards prior to initiating treatment with acalabrutinib. Subjects who are considered to be at risk of TLS (e.g., subjects with a high tumor burden and/or a high circulating lymphocyte count [> 25 x 10^9/L] and/or renal impairment [creatinine clearance <70 mL/min]) should receive prophylaxis. Prophylaxis should consist of adequate hydration and administration of uricostatics (e.g., allopurinol) or a suitable alternative such as a urate oxidate (e.g., rasburicase), before the infusion of obinutuzumab. All subjects considered at risk should be carefully monitored during the initial days of treatment with a special focus on renal function, potassium, and uric acid values. Any additional guidelines according to standard practice should be followed. For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated. Subjects should continue to receive repeated prophylaxis before each subsequent infusion, if deemed appropriate. **Prohibited Concomitant Therapy** Any chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy for treating CLL are prohibited if being used to treat the disease initially under study. 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 underlying CLL are not allowed on study. Warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon) are prohibited. **Acalabrutinib and Concomitant Therapy** The effect of agents that reduce gastric acidity (e.g., antacids or proton-pump inhibitors) on acalabrutinib absorption was evaluated in a healthy volunteer study (ACE-HV-004). Results from this study indicate that subjects should avoid the use of calcium carbonate containing drugs or supplements for a period of at least 2 hours before and at least 2 hours after taking acalabrutinib. Use of omeprazole or esomeprazole or lansoprazole or any other proton-pump inhibitors while taking acalabrutinib is not recommended due to a potential decrease in study drug exposure (see Section 6.5.3 for more detailed information). However, the decision to treat with proton-pump

	inhibitors during the study is at the investigator's discretion, with an understanding of the potential benefit to the subject's gastrointestinal condition and a potential risk of decreased exposure to acalabrutinib. Although the effect of H2receptor antagonists (such as famotidine or ranitidine) on acalabrutinib- absorption has not been evaluated, if treatment with an H2-receptor antagonist is required, the H2-receptor antagonist should be taken approximately 2 hours after an acalabrutinib dose. Concomitant use of strong inhibitors/inducers of CYP3A should be avoided when possible (see Section 6.5.2 for more detailed information).
Safety Plan:	The safety of this study will be monitored by an independent Data Monitoring Committee (DMC). The independent DMC will be chaired by a physician with expertise in CLL. An early safety analysis will be performed by the DMC after 60 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 DMC will review data and provide recommendations regarding stopping or continuing the trial in accordance with the DMC charter.
Statistical Methods and Data Analysis:	All efficacy analyses will be performed using the intent-to-treat (ITT) population. **Primary Efficacy Analysis:** Analysis of the PFS endpoint is event-driven and will be conducted when enrollment is completed and approximately 167 events have occurred in Arms A and B. PFS will be assessed between Arm A versus Arm B using a stratified 2-sided log-rank with the strata used for randomization (17p del: present or absent; ECOG performance status: 0, 1 or 2, and geographic region: North America and Western Europe or Other). The hazard ratio (HR) and its 95% confidence interval (CI) will be computed from a stratified Cox regression model. **Secondary Endpoints and Analysis:** Arms A and C will be compared for PFS in a manner similar to the method described for the primary analysis. The following 2 secondary outcomes will be assessed by comparing the proportions in Arms A and B and Arms A and C using a Cochran-Mantel-Haenszel test stratified by the randomization strata: • ORR defined as achieving CR, CRi, nPR, or PR per IWCLL 2008 criteria. The following 2 secondary outcomes will be assessed for Arms A vs B and Arms A vs C in a manner similar to the method used for PFS:

	• TTNT (defined as the time from randomization to institution of non-protocol-specified treatment for CLL). • OS The Statistical Analysis Plan (SAP) will describe the methodology to be used to maintain Type I error rate control. **Safety Analysis:** Detailed tabulations of safety data (AEs and clinical laboratory tests) will be provided for all subjects receiving the study drug. The number and percent of subjects with treatment-emergent adverse events (TEAEs) will be summarized. Summary of other safety parameters by treatment group will be provided where appropriate.
Interim Analysis:	An interim analysis will be conducted to assess superiority futility of Arm A when compared with Arm B with respect to the primary efficacy endpoint, PFS. The analysis will occur when approximately two-thirds (e.g., 111 total PFS events across Arms A and B) of the outcomes in Arms A and B have occurred. CCI [redacted]
Sample Size:	The study is expected to enroll approximately 510 subjects. Subjects will be randomized in a 1:1:1 ratio so that 170 subjects enter each of Arms A, B, and C. The study is sized to achieve approximately 90% power to detect a hazard ratio of 0.60 in PFS which, under the model assumptions, CCI [redacted] at the 2-sided significance level of 0.05. This sample size calculation was performed assuming CCI [redacted] in Arm A (Goede 2014).

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ABBREVIATIONS AND DEFINITIONS

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11q del	chromosome deletion 11 q
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17p del	chromosome deletion 17p13.1
ACP-196	Acalabrutinib
ADCC	antibody-dependent cell-mediated cytotoxicity
AE(s)	adverse event(s)
AESI	adverse event of special interest
AIHA	autoimmune hemolytic anemia
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HBc	hepatitis B core antibody
Anti-HBs	hepatitis B surface 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
AUC_{0-last}	area under the plasma concentration-time curve from time 0 to time t, where t is the last measurable concentration
BCR	B-cell receptor
BID	twice per day
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
CIRS-G	Cumulative Illness Rating Score-Geriatric
CL/F	oral clearance

Abbreviation	Definition
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed drug concentration
CNS	central nervous system
CR	complete remission (response)
CRF	case report form
CRi	CR with incomplete bone marrow recovery
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLT	dose-limiting toxicity
DCO	data cutoff
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capturing
eGFR	estimated glomerular filtration rate
EGFR	epidermal growth factor receptor
CCI	[redacted]
ET	early termination
CCI	[redacted]
FcR	Fc receptor
FDA	Food and Drug Administration
CCI	[redacted]
FSH	follicle-stimulating hormone
GCLLSG	German CLL study group
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GI	Gastrointestinal
GLP	Good Laboratory Practice
hERG	human ether-à-go-go-related gene
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus

Abbreviation	Definition
HDPE	high-density polyethylene
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
IGHV	immunoglobulin heavy-chain variable
IND	Investigational New Drug
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	Infusion-related reaction
ITP	idiopathic thrombocytopenic purpura
ITT	intent-to-treat
IUD	intrauterine device
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
CCI [redacted]	
MRI	magnetic resonance imaging
CCI [redacted]	
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NDA	New Drug Application
NHL	non-Hodgkin lymphoma
NK	natural killer (cells)

Abbreviation	Definition
NOAEL	no observable adverse effect level
nPR	nodular partial remission
ORR	objective response rate or overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PFS	progression free survival
CCI	CCI
PLL	prolymphocytic leukemia
PML	progressive multifocal leukoencephalopathy
PO	per os (by mouth, orally)
PR	partial remission (response)
PRL	partial remission (response) with lymphocytosis
CCI	CCI
QD	once per day
QM	every month
QTc	corrected QT interval
R/R	relapsed/refractory
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SD	stable disease
SFU	safety follow up
SmPC	Summary of Product Characteristics
SUSAR	suspected unexpected serious adverse reaction
TEAE(s)	treatment-emergent adverse events
TLS	tumor lysis syndrome
T_{max}	time to maximum drug concentration
TTNT	time to next treatment
ULN	upper limit of normal
US	United States
Vz/F	volume of distribution
WBC	white blood cell (count)

1 BACKGROUND INFORMATION

1.1 Front Line Treatment for Elderly Patients with CLL

Chronic lymphocytic leukemia (CLL) is a malignancy of B cells that predominantly affects the older population. CLL has a variable clinical course, where many patients do not require treatment for years and have survival equal to age matched controls. Other patients, however, exhibit aggressive disease and have a poor prognosis despite appropriate therapy (Byrd 2004). While patients with early disease have not been shown to have a survival advantage with early treatment, most patients will eventually require therapy for their disease with the onset of symptoms or cytopenias. Despite the relatively long life expectancy for early stage disease, CLL remains an incurable disease.

The treatment of CLL has progressed significantly over the previous decades. While alkylator therapy was used in the past (O'Brien 1995), randomized trials have demonstrated a higher response rate and longer PFS with fludarabine and subsequently with fludarabine- and cyclophosphamide-based combinations in young, fit patients with CLL (Johnson 1996, Rai 2000, Leporrier 2001, Eichhorst 2006, Catovsky 2007, Flinn 2007). At the same time, the chimeric anti-$CD20^+$ monoclonal antibody, rituximab was introduced for the treatment of CLL (Byrd 2001, O'Brien 2001). The efficacy of rituximab has been improved by combining it with traditional cytotoxic agents such as fludarabine (Byrd 2003, Byrd 2005) or fludarabine plus cyclophosphamide (Wierda 2005), which have produced high CR rates and extended PFS compared with historical controls. A large randomized clinical trial, reported by the German CLL study group (GCLLSG), has shown the benefit of the addition of rituximab to fludarabine and cyclophosphamide in PFS and OS in patients with previously untreated CLL (Hallek 2010).

While fludarabine-based chemoimmunotherapy is standard for treatment-naive younger/fitter patients with CLL, the therapy for older patients or patients with co-morbidities is less well defined. In the large Phase 2 and 3 trials outlined previously, median ages were typically in the early-60s, while the average age of patients diagnosed with CLL is 72 years, which calls into question whether these results are generalizable to the entire CLL population. In fact, a randomized Phase 3 trial investigating primary CLL therapy (fludarabine vs chlorambucil) demonstrated that in patients ≥ 65 years of age, fludarabine was not superior to chlorambucil (Eichhorst 2009). This finding was corroborated by a large retrospective study of front-line trials performed by the Alliance for Clinical Trials in Oncology, which confirmed that fludarabine is not superior to chlorambucil in older patients and also showed that the addition of rituximab to chemotherapy was beneficial regardless of age (Woyach 2013).

Recently, the type II glycoengineered CD20+ monoclonal antibody, obinutuzumab, was introduced. In a Phase 1 trial in patients with previously treated CLL, obinutuzumab had a 62% response rate including a CCI negative CR, suggesting that obinutuzumab may be more active in CLL than rituximab (Morschhauser 2009). The GCLLSG recently completed a Phase 3 trial of rituximab + chlorambucil or obinutuzumab + chlorambucil vs chlorambucil alone in patients with previously untreated CLL and significant comorbidities. In this population, obinutuzumab + chlorambucil (but not rituximab + chlorambucil) improved OS over chlorambucil alone (HR 0.41, p=0.002), and obinutuzumab + chlorambucil improved PFS over rituximab + chlorambucil CCI vs 15.2 months, p<0.001) (Goede 2014). On the basis of these favorable data, the combination of obinutuzumab + chlorambucil has received regulatory approval as frontline therapy for CLL patients.

1.2 BTK inhibition in CLL

In February 2014, ibrutinib (IMBRUVICA®) monotherapy, the first Bruton tyrosine kinase (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=0.22), 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 aged ≥ 65 years (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).

In March 2016, ibrutinib monotherapy was also approved in the United States as a first-line treatment for patients with CLL (IMBRUVICA® package insert).

Important safety risks observed with ibrutinib can be found in the package insert and include the following adverse reactions (IMBRUVICA® package insert):

- Fatal and non-fatal infections
- Atrial fibrillation and atrial flutter

- Other malignancies
- Fatal bleeding events
- Cytopenias (including anemia, neutropenia, and thrombocytopenia)
- Hypertension
- Tumor lysis syndrome
- Embryo-fetal toxicity

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

- Ibrutinib is a potent covalent inhibitor of epidermal growth factor receptor (EGFR); acalabrutinib is not (Section 1.3.2).
- 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 1.3.4) 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 1.3.5).

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 (ACE-CL-007) will investigate whether acalabrutinib in combination with obinutuzumab (Arm B) is superior, based on centrally determined, independently reviewed PFS, to obinutuzumab in combination with chlorambucil (Arm A) and whether acalabrutinib

monotherapy (Arm C) is superior, based on centrally determined, independently reviewed PFS, to obinutuzumab in combination with chlorambucil (Arm A) in subjects with previously untreated CLL. In addition, the study aims to evaluate safety and tolerability of Arms A versus B and Arms A versus C.

1.3 Preclinical Studies

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

1.3.1 CCI

CCI

[redacted]

1.3.2 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.

1.3.3 Dog Lymphoma Study

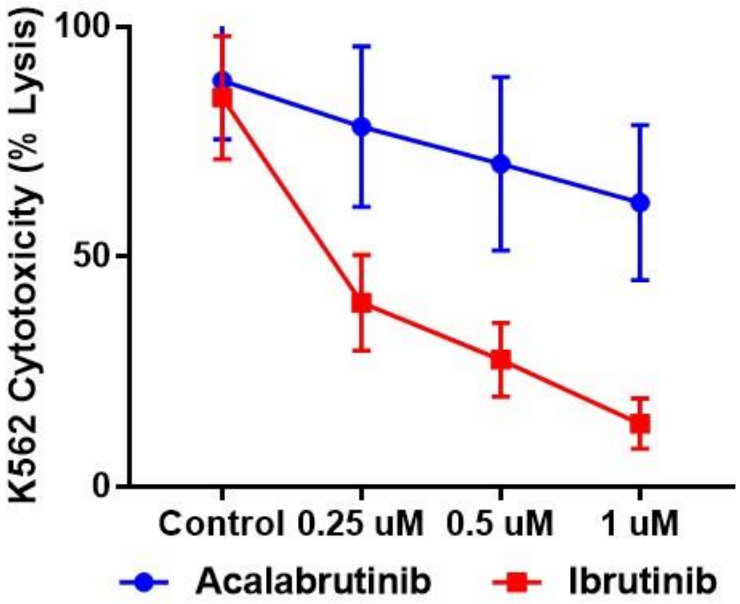
Spontaneous canine B-cell lymphoma shares many characteristics with human non-Hodgkin lymphoma (NHL), including diagnostic classifications and response to BTK inhibition (Honigberg 2010). The life expectancy in untreated animals with aggressive disease is approximately 6 weeks, thus enabling rapid assessment of drug efficacy (Vail 2004). Acalabrutinib was evaluated in an ongoing study in canine spontaneous B-cell lymphoma (Harrington 2016). Twenty dogs were enrolled in the clinical trial and treated with acalabrutinib at dosages of 2.5 to 20mg/kg every 12 or 24 hours. Acalabrutinib was generally well tolerated, with adverse events consisting primarily of grade 1 or 2 anorexia, weight loss, vomiting, diarrhea and lethargy. Per

Veterinary Cooperative Oncology Group criteria for assessment of response in peripheral nodal lymphoma (Vail 2010), ORR was 25% (5/20) with a median progression free survival (PFS) of 22.5 days. Clinical benefit was observed in 30% (6/20) of dogs. These findings suggest that acalabrutinib is safe and exhibits activity in canine B-cell lymphoma patients and support the use of canine lymphoma as a relevant model for human NHL. These findings are similar to the clinical responses observed with ibrutinib in dogs with spontaneous B-cell lymphoma (Honigberg 2010).

1.3.4 Acalabrutinib and Antibody-dependent Cell-mediated Cytotoxicity

As acalabrutinib is not an inhibitor of ITK kinase, it is expected to have less activity against non-malignant cells that require ITK for development and functional activation, such as T and NK cells. ITK kinase is required for Fc receptor (FcR)-stimulated NK cell function including calcium mobilization, granule release (Khurana 2007), and overall antibody-dependent cell-mediated cytotoxicity (ADCC). Anti-$CD20^+$ antibodies are standard of care drugs, often as part of combination regimens, for the treatment of $CD20^+$ B-cell malignancies; obinutuzumab has been specifically designed to increase Fc interactions and promote ADCC and phagocytosis of malignant $CD20^+$ cells. Ibrutinib has been evaluated for effects on NK activity, including ADCC, using in vitro assays of cytokine release, lytic granule release, and cellular cytotoxicity (Kohrt 2014). In contrast to more specific BTK inhibitors, ibrutinib inhibited all these NK cell functions, and impaired NK activity against rituximab-coated autologous CLL cells and in mouse tumor models requiring Fc-mediated effector functions (Kohrt 2014). Acalabrutinib was tested in ADCC and natural cytotoxicity assays, using cells from healthy donors. In these in vitro tests, NK cell function was preserved with acalabrutinib treatment, whereas ibrutinib inhibited functional activity, including natural cytotoxicity against K562 cells.

Figure 1-1. NK Cell Natural Cytotoxicity

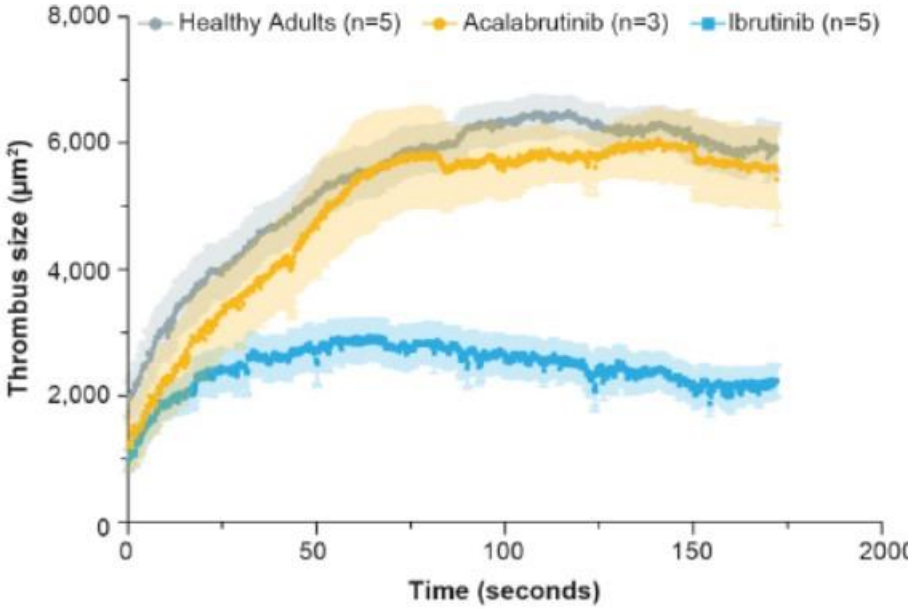


Peripheral blood mononuclear cells were cultured with ^{51}Cr labelled K562 targets at an E:T ratio of 100:1 for 4 hours. Cytotoxicity was evaluated by scintillation counting of supernatants. Treatment, dose and interaction effect were significant in 2-way ANOVA (n = 5 healthy donors; ibrutinib v. acalabrutinib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

1.3.5 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 thrombus formation by using the in vivo human thrombus formation in VWF^{HA1} murine model, which has been previously described (Chen 2008). The in vivo function of platelets isolated from blood of healthy volunteers (n = 5), CLL patients treated with 420 mg QD ibrutinib (n = 5) or CLL patients treated with 100 mg BID acalabrutinib (n = 3) was evaluated in the VWF^{HA1} model. Results from this study showed a reduction in platelet-vessel wall interactions of platelets from ibrutinib-treated CLL patients, but not of those from CLL patients treated with acalabrutinib (Byrd 2016).

Figure 1-2. In Vivo Thrombus Formation



Platelets from patients treated with ibrutinib 420 mg once per day (QD) (n = 5) or acalabrutinib 100 mg twice per day (BID) (n=3) were evaluated for their ability to support thrombus formation in laser injured arterioles of VWF^{HA1} mice. Freshly isolated platelets from healthy volunteers (n=5) were used as non-drug treated controls. A minimum of 4 arterioles per mouse was used to assess thrombus formation for each patient/volunteer sample. Median fluorescence intensity as a function of time is provided in the figure (shading denotes standard error of the median).

1.3.6 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 4.5 µM, suggesting a low clinical risk of off-target effects.

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

Acalabrutinib was well tolerated in standard in vivo Good Laboratory Practice (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 telemetered 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 (including QT interval) parameters. The results suggest that acalabrutinib is unlikely to cause serious off-target effects or adverse effects on critical organ systems.

1.3.7 Drug-drug Interaction Potential

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

Please refer to Section 6.5 for guidance on drugs that may cause drug-drug interactions.

1.3.8 In Vivo General Toxicology

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

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

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

In rats and dogs, no adverse ECG or histopathologic cardiovascular effects were noted at the planned conclusion of the sub-chronic dog studies or in histopathologic endpoints of rats that survived treatment phase in sub-chronic rat toxicity studies. However, in 5 of 6 rats from the 4-week study that died early, slight to moderate necrosis of the myocardium and/or white blood

cell infiltration/inflammation of the myocardium were noted on microscopic examination of the hearts.

1.4 Clinical Studies

1.4.1 CCI and Pharmacodynamics of Acalabrutinib in Healthy Volunteers

ACE-HV-001 was a CCI pharmacodynamic, 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 CCI pharmacodynamics 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 electrocardiogram (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, CCI 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 drug 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 area under the plasma concentration-time curve from time 0 to the 12-hour time point (AUC_{0-12}), area under the plasma concentration-time curve from time 0 to the 24-hour time point (AUC_{0-24}) or area under the plasma concentration-time curve from time 0 to infinity (AUC_{0-inf}), the mean values increased in a dose proportional manner based on the increases of the total dose administered. Mean half-life 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 CCI 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 CCI 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 184L). No differences in half-life values were observed (3.3 vs 2.5 hours).

The pharmacodynamics 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 B-cell receptor (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%).

1.4.2 Clinical Experience of Acalabrutinib in CLL

Acalabrutinib has been studied in a broad range of clinical studies, including subjects with hematologic malignancies and solid tumors. The safety data of acalabrutinib monotherapy are consistent among studies. For more detailed and updated information on the clinical experience for acalabrutinib, please refer to the Acalabrutinib Investigator Brochure.

This section briefly summarizes data from ACE-CL-001 (NCT02029443), an ongoing non-randomized, sequential group, dose-escalation Phase 1/2 study in subjects with

relapsed/refractory (R/R) or previously untreated CLL, Richter's syndrome, or prolymphocytic leukemia (PLL). Subjects received up to 400 mg of acalabrutinib daily.

Preliminary efficacy data for ACE-CL-001 based on subjects with R/R CLL (N=134 as of 01 December 2017), treatment-naive subjects (N=99 as of 04 September 2018), ibrutinib-intolerant subjects (N=33 as of 03 April 2018), and subjects with Richter's syndrome or PLL transformation (N=29 as of 01 December 2017) have been evaluated for tumor response based on International Working Group response criteria (Hallek 2008) as updated (Cheson 2012) to include partial response (PR) with treatment-induced lymphocytosis (PRL). Median time on study for the R/R, treatment-naive, ibrutinib-intolerant, and Richter's syndrome populations were 31.8, 41.6, 19.0, and 2.8 months, respectively. Overall response rate (ORR) for the 4 populations were 96.2%, 99.0%, 80.6%, and 40.7%, respectively. Progressive disease was experienced by 14.9%, 2.0%, 12.1%, and 65.5% of subjects in the R/R, treatment-naive, ibrutinib-intolerant, and Richter's syndrome populations, respectively. Preliminary safety data indicate the regimen is well tolerated (refer to the Acalabrutinib Investigator Brochure).

1.5 Summary and Conclusions

This study (ACE-CL-007) will evaluate the safety and activity of the potent, small-molecule BTK inhibitor, acalabrutinib alone or in combination with obinutuzumab, versus obinutuzumab in combination with chlorambucil in subjects with previously untreated CLL. 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 (i.e., 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 administered 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 rapid reduction and/or resolution of lymphocytosis.

2 STUDY RATIONALE

This randomized controlled Phase 3 study in previously untreated subjects with CLL is designed to determine whether treatment with acalabrutinib in combination with obinutuzumab (Arm B) results in a clinically significant improvement in PFS as compared with treatment with obinutuzumab in combination with chlorambucil (Arm A), and whether treatment with

acalabrutinib monotherapy (Arm C) results in a clinically significant improvement in PFS as compared with treatment with Arm A.

2.1 Dose Selection Rationale for Acalabrutinib

Preliminary CCI data from ACE-CL-001 as described in Section 1.4.2 suggests a plateauing of exposure after 250 mg QD. Pharmacodynamic 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 CCI pharmacodynamic 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 Selection of Obinutuzumab in Combination with Chlorambucil as Comparator

Obinutuzumab is a type II humanized $CD20^{+}$ monoclonal antibody. In preclinical studies, obinutuzumab, as compared with rituximab, has shown superior efficacy by inducing direct cell death and enhanced ADCC (with less complement-dependent toxicity) (Goede 2014). Moreover, a recent Phase 3 clinical trial by the GCLLSG (CLL 11) was completed comparing obinutuzumab in combination with chlorambucil to rituximab in combination with chlorambucil in terms of PFS and ORR in patients with CLL and comorbidities (Cumulative Illness Rating Scale > 6 or a creatinine clearance of 30 to 69 mL per minute). CCI as confirmed by the IRC, was CCI in the obinutuzumab plus chlorambucil arm as compared with 14.9 months with rituximab in combination with chlorambucil HR=0.42 (95%CI: 0.33-0.54), p<0.0001 (GAZYVARO® Summary of Product Characteristics). Importantly, the combination of obinutuzumab and chlorambucil achieved a statistically significant improvement in the CCI negative rate in the bone marrow of 19.5% of subjects whereas only 2.6% of the subjects in the rituximab plus chlorambucil arm achieved CCI negative status in the marrow (p<0.001) (Goede 2014). This Phase 3 study has established the combination of obinutuzumab with chlorambucil as an acceptable standard of care in patients for whom fludarabine-based chemoimmunotherapy is not an acceptable option (National Comprehensive Cancer Network [NCCN] Guidelines Version 1.2016). The most frequent Grade 3 or higher AEs with obinutuzumab in combination with chlorambucil are: neutropenia 35%, infusion related reaction 21%, thrombocytopenia 11%, and infections 2%.

2.3 Combination Therapy with a BTK Inhibitor Plus CD20+ Monoclonal Antibody

The combination of ibrutinib and the CD20+ monoclonal antibodies ofatumumab or rituximab are currently being evaluated in patients with relapsed CLL in 3 separate trials of which 2 have published results as follows:

- A Phase 1b/2 study of ibrutinib (420 mg) and ofatumumab in patients with CLL, small lymphocytic leukemia, prolymphocytic leukemia, or Richter's syndrome has enrolled 3 time-sequential cohorts (Jaglowski 2014). In the first cohort of 27 patients, ibrutinib began on Day 1, Week 1 while ofatumumab began with 300 mg on Week 5, 2000 mg/week for Weeks 6 to 12 and then monthly for 4 months. All 27 subjects completed the first month of therapy without a dose-limiting toxicity (DLT). Of the 24 subjects with CLL, all attained a PR (100%) with 23 subjects remaining on treatment and 1 proceeding to a non-myeloablative stem cell transplant. Infusion toxicities with ofatumumab were more modest than expected. Cohorts administering ofatumumab either concurrently or before ibrutinib have also been completed. However, either early toxicity (concurrent schedule) or early progression (ofatumumab-first arm) have resulted in choosing the run-in arm with ibrutinib for 1 month followed by addition of ofatumumab for a future study.
- Another Phase 2 trial has evaluated rituximab and ibrutinib in patients with high-risk CLL. Rituximab and ibrutinib were administered concurrently beginning in Cycle 1, with 4 doses of weekly rituximab and then monthly administration for a total of 6 cycles. In this trial, toxicities were modest, and responses were seen at an earlier time point than expected from single-agent therapy (Burger 2012).

2.4 Justification for a Trial Combining Acalabrutinib with Obinutuzumab

Bruton tyrosine kinase inhibition is currently transforming the treatment of CLL. While patients appear to be having durable responses, very few responses are CRs, which suggests that drug discontinuation will not be an option. The combination of BTK inhibition with CD20+ antibody therapy is appealing to expedite and potentially deepen remissions. Of the CD20+ antibodies available, obinutuzumab appears to be the most effective, and has shown the potential to induce complete and even CCI negative responses. While ibrutinib is a BTK inhibitor with robust efficacy and safety data, the negative effect of ibrutinib on NK function (Section 1.3.4) has important implications for combining ibrutinib with anti-CD20+ monoclonal antibodies. This justifies exploration of more selective BTK inhibitors, such as acalabrutinib, to optimize the addition of CD20+ monoclonal antibodies to BTK inhibitor therapy.

2.5 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; Section 1.4.2), no DLTs were identified at any evaluated dosages, which included dosages up to 400 mg QD or

100 to 200 mg BID. The ORR in the evaluable subjects for this study is 95% (Byrd 2016). In summary, the preliminary data suggest that acalabrutinib is well tolerated and has robust activity as a single agent in the treatment of subjects with CLL. In addition, CCI pharmacodynamic results show the 100-mg BID regimen produces optimal target coverage over 24 hours (i.e., more complete coverage of de novo synthesis of BTK), which may provide greater clinical benefit than the QD regimen of ibrutinib.

3 STUDY OBJECTIVES

3.1 Primary Objective

- To evaluate the efficacy of obinutuzumab in combination with chlorambucil (Arm A) compared with acalabrutinib in combination with obinutuzumab (Arm B), based on IRC assessment of PFS per CCI criteria, in subjects with previously untreated CLL.

3.2 Secondary Objectives

- To evaluate the efficacy of obinutuzumab in combination with chlorambucil (Arm A) versus acalabrutinib monotherapy (Arm C) based on IRC assessment of PFS per CCI
- To compare obinutuzumab plus chlorambucil (Arm A) versus acalabrutinib plus obinutuzumab (Arm B), and obinutuzumab plus chlorambucil (Arm A) versus acalabrutinib monotherapy (Arm C) in terms of:
  - IRC-assessed objective response rate (ORR) per CCI
  - TTNT (defined as the time from randomization to institution of non-protocol specified treatment for CLL); and
  - OS.

3.3 Safety Objective

Incidence of AEs and SAEs and changes in laboratory measurements.

3.4 Exploratory Objectives

CCI

CCI

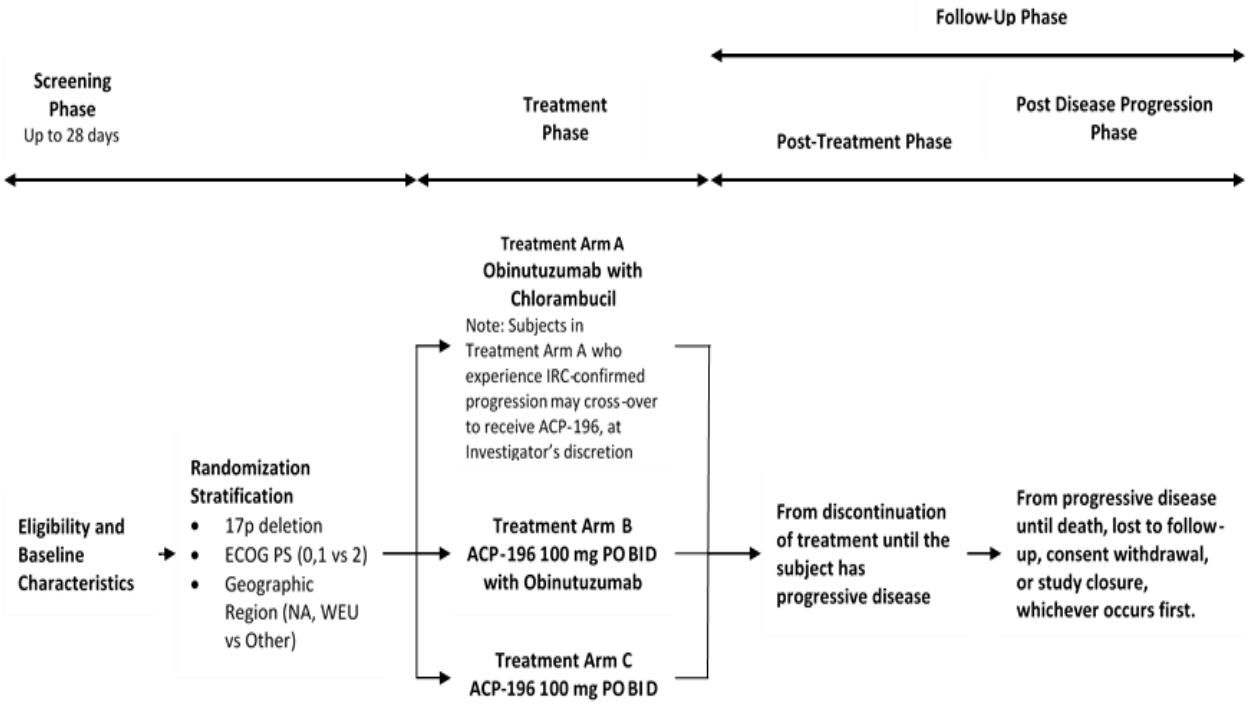
[redacted]

4 STUDY DESIGN

This randomized, multicenter (i.e., approximately 200 global centers), open-label, 3-arm Phase 3 study is designed to evaluate the safety and efficacy of Arm A, Arm B, and Arm C in subjects with previously untreated CLL.

Approximately 510 eligible subjects will be randomized in a 1:1:1 ratio into 3 arms (n=170 each) to receive either Arm A (obinutuzumab in combination with chlorambucil per the package inserts), Arm B (acalabrutinib 100 mg BID in combination with obinutuzumab per the package insert), or Arm C (acalabrutinib 100 mg BID).

Figure 4-1. Study Schema



Abbreviations: BID = twice per day, ECOG = Eastern Cooperative Oncology Group; IRC = Independent Review Committee; NA = North America; PO = oral; PS = performance status; WEU = Western Europe.

This study will use 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 (e.g., demographic and baseline characteristics) are evenly balanced, and to enhance the validity of statistical comparisons across treatment groups. Eligible subjects will be stratified with regard to:

- The presence or absence of 17p del by central laboratory;
- ECOG PS 0, 1 versus 2; and
- Geographic region (North America and Western Europe vs Other).

4.1 Treatment Arm A: Obinutuzumab in Combination with Chlorambucil

Obinutuzumab IV infusions will be administered over a total of 6 treatment cycles. On Cycle 1 Day 1, subjects will receive obinutuzumab 100 mg. On Cycle 1 Day 2, subjects will receive 900 mg. On Cycle 1 Days 8 and 15, subjects will receive 1000 mg. On Day 1 of Cycles 2 to 6, subjects will receive 1000 mg.

Chlorambucil will be orally administered at a dose of 0.5 mg/kg on Days 1 and 15 of Cycles 1 through 6.

Note: A pre-planned interim analysis was performed and met the primary objective. After the interim analysis and per Amendment 6.0, at investigator discretion, subjects randomized to Arm A, who have IRC-confirmed progressive disease (PD) (through Amendment 5.0) or investigator-assessed PD (Amendment 6.0) will be eligible to receive crossover treatment with single-agent acalabrutinib at 100 mg BID until disease progression or unacceptable toxicity. However, the investigator-assessed PD must be confirmed by the study Medical Monitor (Amendment 6.0).

4.2 Treatment Arm B: Acalabrutinib BID in Combination with Obinutuzumab

Acalabrutinib will be orally administered at 100 mg BID starting on Cycle 1 Day 1. Daily administration of acalabrutinib will continue until disease progression or unacceptable toxicity.

Obinutuzumab will be administered as described above for Arm A, starting on Cycle 2 Day 1 for a maximum of 6 cycles.

4.3 Treatment Arm C: Acalabrutinib BID Monotherapy

Acalabrutinib will be orally administered at 100 mg BID starting on Cycle 1 Day 1, and will continue until disease progression or unacceptable toxicity.

4.4 Crossover

Subjects eligible to cross over to acalabrutinib monotherapy will receive acalabrutinib treatment if they meet eligibility for crossover. Eligibility for crossover includes meeting the criteria for ECOG performance status and the laboratory parameters as outlined in the inclusion criteria. Screening for eligibility for crossover, and trial assessments during crossover, are described in Appendix D and may occur concurrently with the study Medical Monitor (Amendment 6.0) and could have occurred concurrently with IRC assessment (through Amendment 5.0) for disease progression. Subjects may not receive any new systemic therapy after IRC confirmation of disease progression (through Amendment 5.0) or investigator-assessed PD confirmed by the study Medical Monitor (Amendment 6.0) along with the initiation of crossover therapy with acalabrutinib. The following de-identified documentation will be reviewed before enrollment to the crossover arm:

- Radiology reports from computed tomography (CT)/magnetic resonance imaging (MRI) documenting measurable nodal disease; CT/MRI from disease progression can be used if within 60 days of crossover dosing Cycle 1 Day 1; and
- CCI [redacted]

4.5 Screening, Treatment, and Follow-up Phases

The subject's eligibility and baseline characteristics will be determined during the Screening Phase. For Arms A, B, and C, the Screening Phase will be up to 28 days before the first dose of study drug and for the crossover arm (Arm D), the Screening Phase will be up to 42 days before the first dose of study drug. The Treatment Phase will extend from the start of randomization until study drug discontinuation. The Post-disease Progression Phase will begin after IRC-confirmed PD (through Amendment 5.0) or investigator-assessed (Amendment 6.0) PD; investigator-assessed PD must be confirmed by the study Medical Monitor. During this phase, subsequent anticancer therapy with start date of therapy, IWCLL indication for treatment initiation, additional malignancy occurrence, and 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.

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 radiological imaging (primary), physical examination or other procedures as necessary, review of hematology 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.

Disease assessments will be done every 12 weeks (± 14 days) with the first on-treatment radiologic assessment occurring on Cycle 4 Day 1, the second on treatment scan on Cycle 7 Day 1, and so on through Cycle 25, and then every 24 weeks (± 14 days) thereafter for all subjects (including subjects who discontinue from the study treatment due to an AE or any reason) until confirmation of disease progression or death, consent withdrawal, or lost to follow-up.

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 the interim analysis results and provide recommendations according to the charter.

One interim analysis using Lan-DeMets alpha spending function based on an O'Brien-Fleming boundary for superiority and futility (non-binding) is planned for the study (see Section 9.4).

The end of trial is defined as the point when the last subject on the study has documented disease progression or death, or has been lost of follow up, whichever occurs first. The anticipated study duration is 4.5 years including enrollment time.

Subjects who are still on treatment at the end of the study (ACE-CL-007) and deriving clinical benefit from acalabrutinib treatment may continue treatment. At the time of the final data cutoff (DCO) and database closure, subjects who remain in this study may be transitioned to a separate rollover study or remain within this study for continued access to study drug. Once all active subjects are eligible to continue to receive acalabrutinib and after database closure, this study will be considered closed. There will be no further data collection other than reporting of SAEs per Section 7.2.2.5. Access within this study will enable continued treatment with visit assessments per standard of care, whereas the separate rollover study will enable treatment continuation with visit assessments and data collection per the rollover study protocol.

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:
    a. ≥ 65 years of age **OR**
    b. > 18 and < 65 years of age, provided that they meet at least one of the following criteria:
        i. Creatinine clearance 30 to 69 mL/min using the Cockcroft-Gault equation
        ii. A score higher than 6 on the CIRS-G (Appendix L).
2. ECOG performance status of 0, 1, or 2.
3. Diagnosis of CD20+ 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. 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 (i.e., ≥ 6 cm below the left costal margin), progressive, or symptomatic splenomegaly.
    c. Massive nodes (i.e., ≥ 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 (e.g., 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 (i.e., ECOG performance status 2; 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.

5. This criterion was deleted as of Protocol Amendment 3.
6. 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 ≥ 50,000 cells/μL (50 x 10^9/L), or ≥ 30,000 cells/μL (30 x 10^9/L) in subjects with documented bone marrow involvement, and without transfusion support 7 days before assessment. Subjects with transfusion-dependent thrombocytopenia are excluded.
    c. Serum AST and ALT/SGPT ≤ 3.0 x ULN.
    d. Total bilirubin ≤ 1.5 x ULN.
    e. Estimated creatinine clearance (i.e., eGFR using Cockcroft-Gault) ≥ 30 mL/min
7. Able to receive all outpatient treatment, all laboratory monitoring, and all radiologic evaluations.
8. 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 18 months after the last dose of obinutuzumab in combination with chlorambucil, whichever is longer. Highly effective forms of contraception are defined in Section 6.4.4.
9. 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 obinutuzumab or chlorambucil, whichever is later. Highly effective forms of contraception are defined in Section 6.4.4.
10. Men must agree to refrain from sperm donation during the study and for 90 days after the last dose of obinutuzumab or chlorambucil, whichever is later.
11. 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 subject privacy regulations). Note vulnerable subjects, as defined in International Conference on Harmonisation (ICH) GCP, are not allowed on this protocol (e.g., prisoners or institutionalized subjects).

5.2 Exclusion Criteria

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

1. Any prior systemic treatment for CLL (note: Prior localized radiotherapy is allowed).
2. Known CNS lymphoma or leukemia.

3. Known prolymphocytic leukemia or history of, or currently suspected, Richter's syndrome.
4. Missing or incomplete documentation of FISH results reflecting the presence or absence of 17p del and the percentage of cells with the deletion in subject records before randomization.
5. 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).
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 WBC count lowering are excluded.
7. Major surgery within 4 weeks before first dose of study drug.
8. 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.
9. 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.
10. 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.
11. 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.
12. Known history of infection with HIV.
13. Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug.
14. 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 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.
15. History of stroke or intracranial hemorrhage within 6 months before randomization.
16. Known history of a bleeding diathesis (e.g., hemophilia, von Willebrand disease).

17. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon) within 7 days of first dose of study drug.
18. Requires treatment with proton-pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole).
19. Breast feeding or pregnant.
20. Current life-threatening illness, medical condition, or organ system dysfunction which, in the Investigator's opinion, could compromise the subject's safety or put the study at risk.
21. Concurrent participation in another therapeutic clinical trial.
22. Requires treatment with a strong CYP3A inhibitor/inducer.
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 Acalabrutinib Investigator Brochure for additional information regarding the drug product to be used in this study.

6.1.2 Obinutuzumab

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

Commercially available obinutuzumab will be supplied as a liquid concentrate (25 mg/mL) for dilution for IV administration. Refer to the local prescribing information for obinutuzumab for further details.

6.1.3 Chlorambucil

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

Commercially available chlorambucil will be supplied as 2-mg film-coated tablets for PO administration. Refer to the local prescribing information for chlorambucil for further details.

6.2 Drug Preparation and Administration

6.2.1 Acalabrutinib in Combination with Obinutuzumab Administration (Arm B)

Acalabrutinib is intended to be administered orally twice daily with 8 ounces (approximately 240 mL) of water. Acalabrutinib may be taken with or without food. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in liquid.

It is recommended that acalabrutinib be taken as close to the scheduled time as possible. If a dose is missed, it can be taken up to 3 hours after the scheduled time with a return to the normal schedule with the following dose. If it has been longer than 3 hours, the dose should not be taken and the subject should take the next dose at the next scheduled time. The missed dose will not be made up and must be returned to the site at the next scheduled time.

Below is the recommended infusion schedule for this study; however, locally approved labelling may be considered for administration of obinutuzumab. Obinutuzumab should be administered as an IV infusion through a dedicated line and under the close supervision of an experienced physician. Obinutuzumab infusions should not be administered as an IV push or bolus.

Dose of obinutuzumab to be administered during 6 treatment cycles each of 28 days duration:

Day of Treatment Cycle		Dose of Obinutuzumab	Rate of Infusion (In the absence of infusion reactions/ hypersensitivity during previous infusions)
First Cycle (loading doses)	Day 1	100 mg	Administer at 25 mg/hr over 4 hours. Do not increase the infusion rate.
	Day 2	900 mg	Administer at 50 mg/hr. The rate of the infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.
	Day 8	1000 mg	Infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.
	Day 15	1000 mg	
Subsequent Cycles	Day 1	1000 mg	

On days when acalabrutinib and obinutuzumab are both administered, the order of study treatment administration will be acalabrutinib followed at least 1 hour later by obinutuzumab.

6.2.2 Obinutuzumab and Chlorambucil Administration (Arm A)

Obinutuzumab will be administered as described above (Section 6.2.1), but starting on Cycle 1 Day 1. Locally approved labelling may be considered for administration of chlorambucil.

Chlorambucil will be orally administered at a dose of 0.5 mg/kg of body weight on Days 1 and 15 of Cycles 1 through 6. Chlorambucil should not be dosed sooner than 14 days from the last dose of chlorambucil. On days when chlorambucil and obinutuzumab are both administered, the order of study treatment administration will be chlorambucil followed by obinutuzumab.

6.2.3 Acalabrutinib Monotherapy Administration (Arm C)

Acalabrutinib monotherapy will be administered as described above (Section 6.2.1).

6.3 Dose Modifications and Delays

6.3.1 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. Dose modification decisions for hematologic toxicity will be based on the grading scale in the Common Terminology Criteria for Adverse Events (CTCAE) v4.03 or higher.

For dose modifications or discontinuation guidance of acalabrutinib in Arm B, Arm C, and Arm D (crossover) see Section 6.3.3. For dose modifications or discontinuation guidance of obinutuzumab or chlorambucil in Arm A and/or Arm B, see Section 6.3.4.

6.3.2 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 (e.g., for drug-related toxicity, surgery, or intercurrent illness) for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. In such circumstances, and if medically appropriate, subjects may resume therapy and relevant clinical, laboratory, and/or radiologic assessments should be done to document whether tumor control can be maintained or whether actual disease progression has occurred.

6.3.3 Dose Modification and Discontinuation for Acalabrutinib

The actions in Table 6-1 should be followed 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.

For subjects on Arm B: If acalabrutinib or obinutuzumab is discontinued, then the other study drug (obinutuzumab or acalabrutinib, respectively) can be continued at the discretion of the investigator (up to a total of 6 cycles of obinutuzumab).

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 QD)
4th	Discontinue acalabrutinib

Abbreviation: QD = once per day.

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.

6.3.3.1 Tumor Lysis Syndrome for acalabrutinib

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

6.3.4 Dose Modification and Discontinuation for Obinutuzumab and Chlorambucil

No reduction in the dose of obinutuzumab is allowed. Recommendations for chlorambucil dose reductions are described below. A dose delay of up to 4 weeks is permitted for obinutuzumab or chlorambucil to allow recovery of hematologic toxicities to ≤Grade 2 or non-hematologic toxicities to Grade 1 or baseline level. If the treatment is delayed for more than 4 weeks, chlorambucil should be discontinued; obinutuzumab may continue at the discretion of the investigator.

For subjects on Arm A: if obinutuzumab or chlorambucil is discontinued, then the other study drug (chlorambucil or obinutuzumab) can be continued at the discretion of the investigator (up to a total of 6 cycles of obinutuzumab or chlorambucil).

Obinutuzumab plus chlorambucil administration on Day 1 of the following cycle will be given if the cytopenia has resolved to Grade ≤2. If the cytopenia persists, obinutuzumab plus

chlorambucil administration will be delayed until the cytopenia has improved to Grade ≤2. If a subject experiences Grade 3 or 4 cytopenia, the guidelines for dose delay and dose reduction are outlined in Table 6-2. Below are the recommended hematologic dose modifications for chlorambucil and obinutuzumab; investigators may also elect to follow appropriate dose modification guidelines in locally approved labeling for these drugs.

Table 6-2. Hematologic Dose Modifications for Obinutuzumab and Chlorambucil

	Chlorambucil	Obinutuzumab
Grade 3 or 4 cytopenia*	Delay dosing for a maximum of 4 weeks. Administer granulocyte colony-stimulating factor (G-CSF) for neutropenia or platelets or red blood cells as required. First episode: If improvement to Grade ≤2 (or baseline), decrease chlorambucil dose to 75% of initial dose for subsequent cycles Second episode: If improvement to Grade ≤2 (or baseline), decrease chlorambucil dose to 50% of initial dose for subsequent cycles Third episode: Discontinue chlorambucil	Delay dose for a maximum of 4 weeks. If improvement to maximum of Grade ≤2 (or baseline), administer full dose. If chlorambucil is discontinued, obinutuzumab may continue at the Investigator's discretion.
Grade 1 or 2 cytopenia*	No dose reduction or delay	No dose reduction or delay

Chlorambucil has been reported to exacerbate or precipitate AIHA and subjects should be monitored carefully for this condition. If a rapid decrease of hemoglobin occurs during therapy, the possibility of chlorambucil- or autoantibody induced hemolysis should be considered and appropriate diagnostic tests (lactate dehydrogenase [LDH], bilirubin, haptoglobin, reticulocytes, Coombs-test) be performed. If hemolysis is suspected a Coomb's test should be performed. If, in the judgment of the treating physician, there is evidence of clinically significant hemolytic anemia secondary to chlorambucil, study treatment should be promptly discontinued. Full details of the hemolytic anemia should be recorded on the AE pages of the CRF.

A subject must discontinue obinutuzumab/chlorambucil if any of the following occur:

- Acute life-threatening respiratory symptoms
- Grade 4 infusion-related symptom – subject must be withdrawn immediately

- Grade 3 infusion-related symptom at rechallenge
- Grade 3 or 4 cytopenia (if not present at baseline) that has not resolved to Grade ≤2 and delays treatment by ≥ 4 weeks
- Grade ≥2 non-cytopenia toxicity that does not resolve to ≤Grade 1/baseline and delays treatment by ≥4 weeks

Refer to the local Summary of Product Characteristics (SmPC) or the local prescribing information for guidance on obinutuzumab/chlorambucil discontinuations.

6.3.5 Premedication Requirements (Obinutuzumab)

6.3.5.1 Infusion-related Reactions

Since some subjects may develop infusion-related reactions to obinutuzumab, premedications must be administered before any obinutuzumab infusions. Complete details on recommended premedications are provided in the obinutuzumab local prescribing information and briefly outlined below:

Obinutuzumab cycles	Subjects requiring premedication	Premedication	Administration
First Cycle: Day 1, Day 2	All subjects	Intravenous glucocorticoid: 20 mg dexamethasone or 80 mg methylprednisolone*	Completed at least 1 hour prior to obinutuzumab infusion.
		650–1000 mg acetaminophen	At least 30 minutes before obinutuzumab infusion.
		Antihistamine (e.g., 50 mg diphenhydramine)	
First Cycle: Day 8, Day 15	All subjects	650–1000 mg acetaminophen	At least 30 minutes before obinutuzumab infusion.
	Subjects with an IRR (Grade ≥1) with the previous infusion	Antihistamine (e.g., 50 mg diphenhydramine)	At least 30 minutes before obinutuzumab infusion.
Subsequent Cycles (total of 6 maximum): Day 1	Subjects with a Grade 3 IRR with the previous infusion OR with a lymphocyte count >25 x 10^9/L prior to next treatment	Intravenous glucocorticoid: 20 mg dexamethasone or 80 mg methylprednisolone*	Completed at least 1 hour prior to obinutuzumab infusion.

Abbreviations: IRR = infusion-related reaction
*Hydrocortisone is not recommended as it has not been effective in reducing the rate of infusion reactions

6.3.5.2 Tumor Lysis Syndrome (Obinutuzumab)

Subjects who are considered to be at risk of TLS (e.g., subjects with a high tumour burden and/or a high circulating lymphocyte count [> 25 x 10^9/L] and/or renal impairment [creatinine clearance < 70 mL/min]) should receive prophylaxis. Prophylaxis should consist of adequate

hydration and administration of uricostatics (e.g., allopurinol) or a suitable alternative such as a urate oxidate (e.g., rasburicase), before the infusion of obinutuzumab. All subjects considered at risk should be carefully monitored during the initial days of treatment with a special focus on renal function, potassium, and uric acid values. Any additional guidelines according to standard practice should be followed. For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.

Subjects should continue to receive repeated prophylaxis before each subsequent infusion, if deemed appropriate.

6.4 Precautions

6.4.1 Risks Associated with Acalabrutinib

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

6.4.1.1 Hemorrhage

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

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

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

6.4.1.2 Infections

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

Across the acalabrutinib clinical development program (including subjects treated with acalabrutinib in combination with other drugs), cases of hepatitis B virus reactivation, aspergillosis, and PML have occurred.

Consider prophylaxis in subjects who are at increased risk for opportunistic infections. Subjects should be monitored for signs and symptoms of infection and treated as medically appropriate.

Subjects with infection events should be managed according to institutional guidelines with maximal supportive care and diagnostic evaluations as clinically indicated.

6.4.1.3 Hepatitis B Reactivation

Cases of hepatitis B virus (HBV) reactivation have been reported in patients treated with acalabrutinib, with 1 case resulting in liver failure and death. Please refer to Section 6.4.3 for monitoring of HBV and management of patients with HBV reactivation.

6.4.1.4 Progressive Multifocal Leukoencephalopathy

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

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

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

If PML is confirmed, permanently discontinue acalabrutinib.

6.4.1.5 Cytopenias

Grade 3 or 4 cytopenias, including neutropenia, anemia, and thrombocytopenia, have occurred in clinical studies with acalabrutinib. Monitor blood counts as medically appropriate.

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

6.4.1.6 Second Primary Malignancies

Second primary malignancies, including solid tumors and skin cancers, have been reported in patients treated with acalabrutinib. The most frequent second primary malignancy was skin

cancer (basal cell carcinoma). Subjects should be monitored for signs and symptoms of malignancy.

Subjects who develop a second primary malignancy should be managed according to institutional guidelines, with diagnostic evaluations as clinically indicated, and it may be necessary for subjects to permanently discontinue study treatment. Continuation of acalabrutinib treatment should be discussed with the Medical Monitor. Please refer to Section 7.2.2.3 for second primary malignancy reporting guidance.

6.4.1.7 Atrial Fibrillation

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

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

6.4.1.8 Dietary Restrictions

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).

Acalabrutinib should be taken with water and may be taken with or without food.

6.4.1.9 Treatment-related Lymphocytosis

Treatment-related lymphocytosis is defined as an ALC > 5000 cells per microliter and an increase above baseline and is associated with agents known to inhibit BCR (Hallek 2008, National Comprehensive Cancer Network [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 (i.e., ≥ 50% increase from baseline and above ALC of 5,000/µL) occurred in 77% of subjects (N=195) in the pivotal Phase 3 CLL study treated with ibrutinib monotherapy. 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.

Note: for complete information on precautions for acalabrutinib refer to the Acalabrutinib Investigator Brochure.

6.4.1.10 Overdose Instructions

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

The Medical Monitor must be contacted if a study drug overdose occurs.

6.4.2 Obinutuzumab and Chlorambucil

For complete information on warnings and precautions, refer to the local prescribing information for obinutuzumab and chlorambucil. A brief summary of warnings and precautions for obinutuzumab is provided below.

6.4.2.1 Progressive Multifocal Leukoencephalopathy

John Cunningham (JC) virus infection resulting in PML, which can be fatal, was observed in patients treated with obinutuzumab. Consider the diagnosis of PML in any subject presenting with new onset or changes to preexisting neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture. Discontinue obinutuzumab therapy and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in subjects who develop PML.

6.4.2.2 Infusion Reactions

Obinutuzumab can cause severe and life-threatening infusion reactions. Two-thirds of patients experienced a reaction to the first 1000 mg infusion of obinutuzumab. Infusion reactions can also occur with subsequent infusions. Symptoms may include hypotension, tachycardia,

dyspnea, and respiratory symptoms (e.g., bronchospasm, larynx and throat irritation, wheezing, laryngeal edema). Other common symptoms include nausea, vomiting, diarrhea, hypertension, flushing, headache, pyrexia, and chills. Refer to Section 6.3.5 for premedication requirements to reduce risk of infusion reactions.

For subjects with any Grade 4 infusion reactions, including but not limited to anaphylaxis, acute life-threatening respiratory symptoms, or other life-threatening infusion reaction: Stop the obinutuzumab infusion. Permanently discontinue obinutuzumab therapy.

For subjects with Grade 1, 2, or 3 infusion reactions: Interrupt obinutuzumab for Grade 3 reactions until resolution of symptoms. Interrupt or reduce the rate of the infusion for Grade 1 or 2 reactions and manage symptoms.

For subjects with pre-existing cardiac or pulmonary conditions, monitor more frequently throughout the infusion and the postinfusion period since they may be at greater risk of experiencing more severe reactions. Hypotension may occur as part of the obinutuzumab infusion reaction. Consider withholding antihypertensive treatments for 12 hours prior to, during each obinutuzumab infusion, and for the first hour after administration until blood pressure is stable. For patients at increased risk of hypertensive crisis, consider the benefits versus the risks of withholding their antihypertensive medication as is suggested here.

6.4.2.3 Tumor Lysis Syndrome

Acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, and/or hyperphosphatemia from TLS can occur within 12 to 24 hours after the first infusion. Refer to Section 6.3.5 for premedication requirements to reduce risk of TLS.

6.4.2.4 Infections

Serious bacterial, fungal, and new or reactivated viral infections can occur during and after obinutuzumab therapy. Fatal infections have been reported with obinutuzumab. Do not administer obinutuzumab to subjects with an active infection. Subjects with a history of recurring or chronic infections may be at increased risk of infection.

6.4.2.5 Neutropenia

Obinutuzumab in combination with chlorambucil caused Grade 3 or 4 neutropenia in 33% of patients in the Phase 3 trial. Subjects with Grade 3 to 4 neutropenia should be monitored frequently with regular laboratory tests until resolution. Anticipate, evaluate, and treat any symptoms or signs of developing infection. Neutropenia can also be of late onset (occurring

more than 28 days after completion of treatment) and/or prolonged (lasting longer than 28 days). Subjects with neutropenia are strongly recommended to receive antimicrobial prophylaxis throughout the treatment period. Antiviral and antifungal prophylaxis should be considered.

6.4.2.6 Thrombocytopenia

Obinutuzumab in combination with chlorambucil caused Grade 3 or 4 thrombocytopenia in 10% of patients in the Phase 3 trial. In 4% of patients, obinutuzumab caused acute thrombocytopenia occurring within 24 hours after the obinutuzumab infusion. Fatal hemorrhagic events during Cycle 1 have also been reported in patients treated with obinutuzumab.

Monitor all subjects frequently for thrombocytopenia and hemorrhagic events, especially during the first cycle. In subjects with Grade 3 or 4 thrombocytopenia, monitor platelet counts more frequently until resolution and consider subsequent dose delays of obinutuzumab and chlorambucil or dose reductions of chlorambucil. Transfusion of blood products (i.e., platelet transfusion) may be necessary. Consider withholding concomitant medications which may increase bleeding risk (platelet inhibitors, anticoagulants), especially during the first cycle.

6.4.2.7 Immunization

The safety and efficacy of immunization with live or attenuated viral vaccines during or after obinutuzumab therapy has not been studied. Immunization with live virus vaccines is not recommended during treatment and until B-cell recovery.

6.4.2.8 Risk of Gastrointestinal Perforation

The sponsor has been notified of the important identified risk of GI perforation with obinutuzumab treatment in patients with NHL by the manufacturer of obinutuzumab (Genentech Inc.). Monitoring of subjects with GI involvement for GI perforation is recommended.

6.4.3 Hepatitis B Virus Reactivation

Serious or life-threatening reactivation of viral hepatitis may occur in subjects treated with a BTK inhibitor (de Jésus Ngoma 2015, FDA Drug Safety Communication 2013). Cases of HBV reactivation have been reported in patients treated with acalabrutinib with 1 case resulting in liver failure and death. HBV reactivation can also occur with anti-$CD20^{+}$ antibody therapy. Therefore, subjects who are hepatitis B core antibody (anti-HBc) positive, or have a known history of HBV infection, should be monitored every month 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.

In subjects who develop reactivation of HBV while receiving obinutuzumab, immediately discontinue obinutuzumab and any concomitant chemotherapy and institute appropriate treatment. Insufficient data exist regarding the safety of resuming obinutuzumab in subjects who develop HBV reactivation.

6.4.4 Reproductive Toxicity

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

Definition of women of non-reproductive potential:

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

- Postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a 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

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

OR

- Have a congenital or acquired condition that prevents childbearing.

Definition of contraception:

- Sexual abstinence† (only if refraining from heterosexual intercourse during the entire period of risk associated with the study treatments);

OR

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

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‡:

Combination method (requires use of a male condom in combination with 1 of the following):

- 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)

Hormonal contraception may be susceptible to interaction with study or other drugs, which may reduce the efficacy of the contraception method. Women using hormonal contraceptives should add a barrier method.

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

‡If a contraceptive method 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.

Pilot reproductive toxicity studies have been performed that evaluate the effects of acalabrutinib on embryofetal development. At acalabrutinib exposures comparable to the clinical exposures at the intended therapeutic dosage, no acalabrutinib-related adverse effects of target organ toxicity, reproductive toxicity, or embryofetal development were identified in the nonclinical safety assessment (see the Acalabrutinib Investigator Brochure).

There are no data from the use of obinutuzumab in pregnant women. Chlorambucil is considered a probable genotoxicant and can cause fetal harm when administered to pregnant women.

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 2 days after the last dose of acalabrutinib or 18 months after the last dose of obinutuzumab and chlorambucil, 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 obinutuzumab or chlorambucil, whichever is later. Men must also refrain from donating sperm during the study and for 90 days after the last dose of obinutuzumab or chlorambucil, whichever is later. In addition, since chlorambucil is probably mutagenic and teratogenic in humans (LEUKERAN® package insert), condom (barrier) use is also required for all male subjects treated with chlorambucil (including vasectomized male subjects) during and up to 90 days after the last dose of chlorambucil to prevent possible direct exposure to a developing fetus (in case of a pregnant female partner).

Female 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 up to 2 days after the last dose of acalabrutinib or 18 months after the last dose of obinutuzumab or chlorambucil, 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 in clinical studies should promptly notify the investigator if they, or their partners, become pregnant during this period. If a woman 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.

6.5 Concomitant Medications

6.5.1 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).

6.5.2 Guideline for Use of CYP-Inhibiting/Inducing Drugs

At the systemic exposure levels expected in this study, acalabrutinib inhibition of CYP metabolism is not anticipated. However, as discussed in Section 1.4.1, concomitant administration of acalabrutinib with a strong CYP3A inhibitor increased exposure by approximately 5-fold. Consequently, the concomitant use of strong inhibitors/inducers of CYP3A (Appendix F) should be avoided when possible. Avoid coadministration of strong CYP3A inducers. If a subject requires treatment with a strong CYP3A inducer, increase the acalabrutinib dose to 200 mg BID during concomitant administration with the strong inducer and return to recommended dose of 100 mg BID after stopping the strong CYP3A inducer.

If the subject requires treatment with a moderate CYP3A inhibitor, the acalabrutinib dose should be reduced to 100 mg QD.

6.5.3 Guideline for Use of Drugs that Affect Gastric pH

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

6.5.4 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.

Steroids used to premedicate or manage obinutuzumab infusion-related reactions are permitted.

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

For additional information on potential drug-drug interactions, refer to the Acalabrutinib Investigator Brochure.

6.6 Treatment Compliance

Subject compliance with acalabrutinib 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 diaries, or pill counts.

7 EFFICACY AND SAFETY PROCEDURES

The Schedule of Assessments are provided in Appendix A, Appendix B, Appendix C, and Appendix D. Descriptions of the scheduled evaluations are outlined below.

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 include information about the study and emergency contact details.

7.1 Description of Procedures

7.1.1 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.

7.1.2 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

CCI 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:

CCI [redacted]

Please refer to the study manual for a more detailed description of the randomization procedures. Treatment with study drug should begin within 7 days of randomization.

7.1.3 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 or Binet staging within 28 days of first dose with study drug, and history of autoimmune CLL complications and their treatment will also be recorded based upon available documents and subject history.

7.1.4 Physical Examination

The physical examination includes height (Screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal, nervous, and lymphatic system and general appearance. 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.

7.1.5 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 (i.e., ECOG performance status 2 or worse; inability to work or perform usual activities);

c. Fevers higher than 100.5°F or 38°C for 2 or more weeks without other evidence of infection; or

d. Night sweats for more than 1 month without evidence of infection

7.1.6 Cumulative Illness Rating Scale-Geriatric (CIRS-G)

CIRS-G (Appendix L) is an indicator of illness severity and comorbidity in older subjects (Extermann 1998). CIRS-G scoring is to be performed by a licensed provider (e.g., physician, physician assistant, or nurse) for subjects > 18 and < 65 years of age.

Rating Strategy

Please see specific scoring guidelines below for each organ system.

0: No Problem.

1: Current mild problem or past significant problem.

2: Moderate disability or morbidity/requires “first line” therapy.

3: Severe/constant significant disability/”uncontrollable” chronic problems.

4: Extremely severe/immediate treatment required/end organ failure/severe impairment of function.

7.1.7 Vital Signs

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

7.1.8 Electrocardiogram

Subjects should be in supine position and resting for at least 10 minutes before the Screening ECG.

7.1.9 ECOG Performance Status

The ECOG performance status index is provided in Appendix E.

7.1.10 Hepatitis Serologies

Hepatitis serology testing must include HBsAg, anti-HBs, anti-HBc, and hepatitis C (HCV) antibody. In addition, any subjects testing positive for anti-HBc , must have PCR testing during screening and on study (see Appendix A, Appendix B, Appendix C, Appendix D, and exclusion criterion #14). Testing will be done by local or central laboratory.

Subjects who are anti-HBc positive should have quantitative PCR testing for HBV DNA performed during screening and every month thereafter during the randomized part of the study,

at screening for crossover, and during crossover. Monthly 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 treatment and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B. As IVIG may cause false positive hepatitis serology, monthly PCR testing is not required in subjects who are currently receiving or received prophylactic IVIG within 3 months before study enrollment and have a documented negative anti-HBc test before the initiation of IVIG therapy. PCR testing should be performed when clinically indicated (e.g., in the setting of rising transaminase levels).

Subjects with a known history of hepatitis C or who are hepatitis C antibody positive should be tested for HCV RNA performed during screening. Refer to Section 6.4 and Appendix A, Appendix B, Appendix C, and Appendix D regarding monitoring of subjects who are anti-HBc positive.

7.1.11 CCI

CCI [redacted]

7.1.12 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.

One sample will be collected for immunoglobulin heavy-chain variable (IGHV and p53 mutational status.

One sample will be collected to study the leukemia cell expression of $CD38^{+}$ and ZAP-70.

CCI [redacted]

CCI

[redacted]

7.1.13 Pregnancy Test

Serum pregnancy tests are required only for women with childbearing potential and may be done by local laboratories. Pregnancy tests will be performed at Screening, on Cycle 1 Day 1, and at the safety-follow-up visit, and may be performed more frequently if required by local regulatory authorities.

7.1.14 Hematology

Hematology will be evaluated by a central laboratory and will include a complete blood count (CBC) with 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.

7.1.15 Determination of T/B/NK Cell Counts

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.

7.1.16 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, LDH, phosphate/phosphorus, potassium, sodium, total bilirubin, and uric acid. Any missing central laboratory blood samples should be redrawn as soon as possible.

7.1.17 Serum Immunoglobulins and β_2-microglobulin

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

7.1.18 CCI

CCI

CCI [redacted]

7.1.19 CCI [redacted]

CCI [redacted]

7.1.20 Bone Marrow Aspirate and Biopsy

7.1.20.1 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.

7.1.20.2 [redacted]/Response Evaluation (more details provided in Appendix G)

If the subject's physical examination findings, laboratory evaluations, and radiographic evaluations suggest that CR has been achieved in all response parameters, a bone marrow aspirate and biopsy and peripheral blood sample must be obtained and sent to the central laboratory for analysis to confirm the CR and [redacted] In cases where cytopenic progression is suspected, a bone marrow aspirate or biopsy should be performed to distinguish autoimmune and drug-related cytopenias.

[redacted]

Arm A: Obinutuzumab + Chlorambucil:

For subjects on treatment with obinutuzumab plus chlorambucil, if the subject's physical examination findings, laboratory evaluations, and radiographic evaluations suggest that CR has been achieved, a confirmatory bone marrow biopsy/aspirate and peripheral blood sample [redacted] For subjects who completed treatment, if the subject's physical examination findings, laboratory evaluations, and radiographic evaluations suggest that CR has been achieved, a confirmatory bone marrow biopsy/aspirate and peripheral blood sample [redacted]

Arm B: Obinutuzumab + Acalabrutinib:

For subjects on obinutuzumab plus acalabrutinib, if the subject's physical examination findings, laboratory evaluations, and radiographic evaluations suggest that CR has been achieved, a confirmatory bone marrow biopsy/aspirate and peripheral blood sample [redacted] For subjects on acalabrutinib monotherapy, if the subject's physical examination findings, laboratory evaluations, and radiographic evaluations suggest that CR has been achieved, a confirmatory

bone marrow biopsy/aspirate and peripheral blood sample [redacted]

Arm C or Crossover Acalabrutinib Monotherapy Arm:

For subjects on acalabrutinib monotherapy, if the subject's physical examination findings, laboratory evaluations, and radiographic evaluations suggest that CR has been achieved, a confirmatory bone marrow biopsy/aspirate and peripheral blood sample t[redacted]

At the discretion of the investigator, a repeat bone marrow biopsy/aspirate and peripheral blood testing [redacted]

7.1.21 CT/MRI Scans

Radiological imaging by CT with contrast is required and must include the pelvis, abdomen, chest, and neck. Subjects who are intolerant to IV CT contrast agents will have CT scans performed with oral contrast. When possible, all subjects should have radiographic tumor measurements done at the participating study center or at an acceptable alternate imaging facility using an identical imaging protocol and similar equipment. The same imaging equipment should be used for all scans whenever possible. The same radiologist should be assigned to read all the scans for a given subject throughout the study as much as possible. MRI may be used 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).

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 at any time (screening and postdose) the liver or spleen are abnormal in size, the cranial-caudal measurement of the spleen and longest diameter of the liver should be assessed by CT/MRI at response evaluations.

In the event disease progression is suspected due to physical examination or laboratory test results, a CT scan must be performed to confirm disease progression. 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.

7.1.22 Medical Resources Utilization

Hospitalizations, emergency department visits, blood product transfusions, and hematopoietic growth factor use will be collected for each treatment arm.

7.1.23 Adverse Events

The accepted regulatory definition for an AE is provided in Section 7.2.1. The AE reporting period is described in Section 7.2.2.1. Important additional requirements for reporting SAEs are explained in Section 7.2.2.6.

7.1.24 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.

7.1.25 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.

7.1.26 Overall Response Evaluations

Response evaluations will be done every 12 weeks (± 14 days) with the first on-treatment radiologic assessment occurring on Cycle 4 Day 1, the second on-treatment scan on Cycle 7 Day 1, and so on through Cycle 25, and then every 24 weeks (± 14 days) thereafter. Response evaluations should be completed during the Treatment Phase and the Post-Treatment Phase, until the subject has progressive disease.

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 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. 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). 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, prior to crossover from Arm A to the crossover arm, a subject may continue treatment and remain under close observation until progression is confirmed by the IRC (through Amendment 5.0) or until disease progression is assessed by the investigator and confirmed by the study Medical Monitor (Amendment 6.0).

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

An ET visit is required for safety assessments for any subjects who permanently discontinue study treatment for any reason (except for death, lost to follow-up, or withdrawal of consent), 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 treatment within 10 days of a scheduled study visit or if the ET visit would be performed within 14 days of the SFU visit. If the SFU visit is within ± 7 days of a regularly scheduled visit during the Post-treatment Phase, the visits may be combined into a single visit.

In addition to the ET 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, Appendix B, Appendix C, and Appendix D for the assessments required for the ET and SFU visits.

7.1.28 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 the time of the interim analysis and 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.

7.1.29 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

7.2.1.1 Adverse Events

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

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with CLL that were not present before the AE reporting period (see Section 7.2.2).
- Pre-existing medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.
- Abnormal laboratory values considered clinically significant by the investigator should be reported as an AE.

The following are NOT considered an AE:

- **Pre-existing condition that has not worsened:** A pre-existing condition (documented on the medical history CRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.
- **Preplanned hospitalization:** A hospitalization planned before signing the ICF is not considered an SAE, but rather a therapeutic intervention. However, if during the

preplanned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before randomization in the study, will not be considered serious if they are performed after randomization in the study for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances are also not SAEs.

- **Diagnostic testing and procedures:** Testing and procedures should not be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported. If a test or procedure is done to rule out a diagnosis, the sign or symptom leading to the test/procedure should be the event term, and the event term should only be updated to the diagnosis if/when the diagnosis is confirmed. Testing and procedures performed solely as screening measures (e.g., routine screening mammography or colonoscopy) should not be reported as AEs or SAEs.
- **Abnormal laboratory results:** Abnormal laboratory results are not AEs unless they are clinically significant. For example, a clinically significant laboratory result is one that requires treatment (for example a blood transfusion for low hemoglobin) or requires a change in study drug (e.g., lowering the dose or withholding study drug while the laboratory finding resolves or stabilizes).
- **Progression of underlying malignancy**: Progression of underlying malignancy will not be reported as an AE if it is clearly consistent with the suspected progression of the underlying cancer. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as an SAE. Clinical symptoms of progression may be reported as AEs if the symptoms cannot be determined as exclusively due to the progression of the underlying malignancy, or if they do not fit the expected pattern of progression for the disease under study.

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

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

7.2.1.2 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 (i.e., 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 (i.e., 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 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.

7.2.1.3 Adverse Events of Special Interest

The following events are adverse events of special interest (AESIs) and must be reported to the sponsors expeditiously (see Section 7.2.2.5 for reporting instructions), irrespective of regulatory seriousness criteria or causality:

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

For study treatment containing biologic products:

- Suspected transmission of an infectious agent by the study drug whereby any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings indicating an infection in a subject exposed to a medicinal product. This term ONLY applies when a contamination of the study drug is suspected, NOT for infections supported by the mode of action, e.g., immunosuppression.

7.2.1.4 Suspected Adverse Reaction

The Food and Drug Administration (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 (e.g., 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 (e.g., 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 (e.g., 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 (e.g., 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 (e.g., 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.

7.2.1.5 Severity

Definitions found in the Common Terminology Criteria for Adverse Events (CTCAE) v4.03 or higher will be used for grading the severity (intensity) of nonhematologic and hematologic 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.

7.2.1.6 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 H for more detail on assessing causality.

7.2.1.7 Unexpected Adverse Events

An "unexpected" AE is an AE that is not listed in the Reference Safety Information for the study drug or is not listed at the specificity or severity that has been observed. The Reference Safety Information for acalabrutinib is the Investigator Brochure. The Reference Safety Information for the comparator drugs is the respective SmPCs. 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 AEs will be reported until 30 days after the last dose of study drug or the start of new anticancer therapy (whichever comes first). After this period, investigators should report SAEs or other AEs of concern that are believed to be related to prior treatment with study drug.

All SAEs 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.

7.2.2.2 Assessment of Adverse Events

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

Each recorded AE or SAE will be described by its diagnostic term, duration (i.e., start and end dates), severity, regulatory seriousness criteria (if applicable), suspected relationship to study drug, and any actions taken. Whenever possible, AEs/SAEs should be reported by diagnosis term not as a constellation of symptoms.

7.2.2.3 Second Primary Malignancies

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

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

7.2.2.4 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 Acerta Pharma Drug Safety. 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 with the subject or with the partner of a treated subject during this study will be reported for tracking purposes only, if agreed to by the subject or the partner of the subject in this study. All pregnancies and partner pregnancies that are identified during or after this study will be reported. All pregnancies and partner pregnancies that are identified during or after this study, wherein the estimated date of conception is determined to have occurred from the time of consent to 2 days after the last dose of acalabrutinib or 18 months after last dose of obinutuzumab in combination with chlorambucil (whichever is longer) must be reported, followed to conclusion, and the outcome reported, as long as the subject or partner has consented to participate in follow-up.

Pregnancy itself is not regarded as an AE unless there is suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Likewise, elective abortions without complications are not considered AEs. Any SAEs associated with pregnancy (e.g., congenital abnormalities/birth defects/spontaneous 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 receiving acalabrutinib who become pregnant must immediately discontinue study drug. The Investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

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

7.2.2.5 Expedited Reporting Requirements for Serious Adverse Events and AESIs

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

Death due to disease progression should be recorded on the appropriate form in the EDC system. If the primary cause of death is disease progression, the death due to disease progression should not be reported as an SAE. If the primary cause of death is something other than disease progression, then the death should be reported as an SAE with the primary cause of death as the event 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 Acerta Pharma Drug Safety, or designee, as outlined above.

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

An SAE may qualify for mandatory expedited reporting to regulatory authorities if the SAE is attributable to the investigational product (or if a causality assessment is not provided for the SAE, in which case a default of “related” may be used for expedited reporting purposes) and the SAE is not listed in the Acalabrutinib Investigator Brochure (i.e., an unexpected event). In this case, Acerta Pharma Drug Safety/Designee will forward a formal notification describing the suspected unexpected serious adverse reaction (SUSAR) to all investigators. Each Investigator must then notify his or her IRB/IEC of the SUSAR.

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

Reference Safety Information

For the purpose of reporting AEs and SAEs:

- The Investigator Brochure contains the Reference Safety Information (RSI) for acalabrutinib
- The respective SmPC contains the RSI for obinutuzumab and chlorambucil

7.2.2.6 Reporting of Serious Adverse Events by Sponsor

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

7.2.2.7 Hy's Law

During the course of the study (ACE-CL-007), the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a subject meets potential Hy's law criteria at any point during the study. All sources of laboratory data are appropriate for the determination of potential Hy's law and Hy's law events; see Appendix M for details.

8 WITHDRAWAL OF SUBJECT FROMTREATMENT OR ASSESSMENT

8.1 Withdrawal of Subjects from Study Treatment

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

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

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 possible 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 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.

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 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.

9.1.1 Independent Review Committee

A physician with expertise in CLL will chair the IRC. The IRC will conduct response evaluations in accordance with its charter.

9.1.2 Data Monitoring Committee

The interim efficacy and overall safety of this study will be monitored by an independent DMC. The independent DMC will be chaired by a physician with expertise in CLL.

An early safety analysis will be performed after approximately 60 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. This information will be reviewed by the Medical Monitor on an ongoing basis until this early safety analysis is conducted.

The DMC will meet and review data approximately every 6 months (24 weeks) and provide recommendations regarding stopping or continuing the trial in accordance with the DMC charter.

9.2 Randomization

This study will use an IWRS for randomization. Approximately 510 eligible subjects will be randomized in a 1:1:1 ratio into 3 arms (n=170 each) to receive either obinutuzumab in combination with chlorambucil per the package inserts (Arm A), acalabrutinib 100 mg BID in combination with obinutuzumab per the package insert (Arm B), or acalabrutinib 100 mg BID (Arm C).

Subjects will be randomized based on the following stratification factors:

- Presence versus absence of 17p del by central laboratory
- ECOG performance status 0, 1 versus 2.
- Geographic region (North America and Western Europe versus Other).

9.3 Determination of Sample Size

The study is expected to enroll approximately 510 subjects. Subjects will be randomized in a 1:1:1 ratio. Thus, approximately 170 subjects will be in each arm.

The study is sized to achieve approximately 90% power to detect a hazard ratio (Arm B/Arm A) of 0.60 for PFS which, under the model assumptions, CCI [redacted] in median PFS time: CCI [redacted] Given the study assumptions, the minimum detectable treatment difference at the final analysis of PFS corresponds to a CCI [redacted]

[redacted]

One final analysis and one interim analysis for PFS are planned. The final analysis of PFS is planned to occur when a total of 167 PFS events have been observed, which is anticipated to occur at CCI [redacted] after the first subject randomized. The interim analysis of PFS will be conducted when approximately two-thirds of the final analysis PFS event goal (i.e., 111 events

across Arms A and B) have been observed, which is expected to occur approximately CCI after the first subjects has been randomized.

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

9.4 Interim Analysis

An interim analysis will be conducted to assess superiority and futility of Arm A vs Arm B with respect to the primary efficacy endpoint, PFS, as assessed by IRC. An event-based interim analysis will occur when approximately two-thirds (e.g., 111 total PFS events across Arms A and B) of the required PFS events for final analysis have occurred. CCI [redacted] The nominal alpha levels for the interim and final analyses will be determined based on the actual number of PFS events observed at the time of the analyses.

All tests for interim and final analyses will be performed at 2-sided significance level. The Lan-DeMets alpha spending function based on the O'Brien-Fleming boundary for superiority and futility (non-binding) will be used. CCI [redacted]

Table 9-1. CCI [redacted]

CCI [redacted]

The nominal α_1 and α_2 levels will be determined based on the actual information fraction at the time of the interim analysis.

If the criteria for early efficacy or futility are met at the time of the interim analysis, the DMC may recommend stopping the study. An independent statistician will conduct the interim analysis for review by the DMC. The DMC will make its recommendation to the Sponsor in accordance with the terms of the DMC charter.

If the interim analysis of the primary endpoint, PFS as assessed by IRC between Arms A and B, meets the significance level, then Arms A and C will be also compared for PFS as assessed by IRC, in a manner that will preserve the overall Type I error rate at a 0.05 level. The SAP will describe the methodology for multiplicity adjustment.

9.5 Final Analysis

The final analysis for PFS as assessed by IRC will be conducted after approximately 167 events across Arms A and B are confirmed by the IRC. The median duration of PFS and the associated 95% CI for each treatment arm will be estimated using the Kaplan-Meier method. The HR and the 2-sided 95% of HR will be estimated using a Cox proportional-hazard model stratified by the randomization strata.

If the primary endpoint is significant, Arms A and C will be tested for PFS as assessed by IRC in a way that maintains the overall 2-sided Type I error rate at a 0.05 level. The SAP will describe the methodology for multiplicity adjustment.

9.6 Analysis Populations

9.6.1 Intent-to-Treat (ITT) Population

The ITT population will be defined as all randomized subjects. 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, as well as baseline and disease characteristics.

9.6.2 Safety Population

The safety population includes all subjects who received ≥ 1 dose of study drug. The safety population will be used for the safety analyses. Subjects will be analyzed as treated.

9.7 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 approaches for other missing data.

9.8 Control for Bias

The following study design components will facilitate the control for bias:

- Large (approximately 510 subjects).

- Multicenter.
- Randomized.

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.

9.9 Efficacy Analyses

9.9.1 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. Subjects who withdraw from the study or are considered lost to follow-up without prior documentation of disease progression will be censored on the date of the last adequate disease assessment. Subjects who start new anticancer therapy before documentation of disease progression will be censored on the date of the last adequate disease assessment that is on or before the start date of the new anticancer therapy. For subjects without an adequate post-baseline disease assessment, PFS will be censored on the date of randomization. The primary efficacy analysis will be performed in the ITT population to compare PFS as assessed by the IRC between Arms A and B treatment arms using a stratified 2-sided log rank test. The distribution of PFS will be summarized for each treatment arm using median and its corresponding 95% CI based on Kaplan-Meier estimates. The estimate of the hazard ratio and its corresponding 95% CI will be computed using a Cox Proportional Hazards model stratified by the randomization strata.

The SAP will describe the sensitivity analyses to be performed.

9.9.2 Secondary Endpoints and Methods

9.9.2.1 PFS

The first secondary endpoint of the study is PFS compared between Arms A and C, where PFS is assessed by IRC review per IWCLL 2008 criteria. The analysis will be performed in the ITT population to compare PFS between Arms A and C using a 2-sided log rank test. The distribution of PFS will be summarized for each treatment arm using median and its corresponding 95% CI based on Kaplan-Meier estimates. The estimate of the hazard ratio and its corresponding 95% CI will be computed using a Cox Proportional Hazards model.

9.9.3 Other Secondary Endpoints

The SAP will describe Type I error control for the secondary outcomes.

The following secondary endpoints will be compared first between Arms A and B and between Arms A and C.

9.9.3.1 Objective Response Rate

ORR is defined as achieving CR, CRi, nPR, or PR per the investigator or IRC assessment per IWCLL 2008 criteria at or before initiation of subsequent anticancer therapy.

ORR will be compared between treatment arms (A vs B and A vs C) using the Cochran-Mantel-Haenszel chi-square test, adjusted for randomization stratification factors.

9.9.3.2 Time to Next Treatment

TTNT (defined as the time from randomization to institution of non-protocol specified treatment for CLL) will be compared between the treatment arms using a 2-sided log rank test. Distribution of PFS will be summarized for each treatment arm using the median and its corresponding 95% CI based on Kaplan-Meier estimates. The estimated HR and its corresponding 95% CI will be computed from a Cox Proportional Hazards model.

9.9.3.3 Overall Survival

The OS analysis will be performed in the ITT population comparing Arms A and B using a 2-sided log rank test. The distribution of OS will be summarized for each treatment arm using the median and its corresponding 95% CI based on Kaplan-Meier estimates. The estimated HR and its corresponding 95% CI will be computed using a Cox Proportional Hazards model stratified by the randomization strata.

9.9.4 Exploratory Endpoints

CCI

[redacted]

CCI

[redacted]

9.10 Safety Analyses

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

9.10.1 Adverse Events

Adverse events will be graded by the Investigator according the National Cancer Institute (NCI)-CTCAE v4.03 or higher for hematologic and nonhematologic AEs. Each AE verbatim term will be coded to a system organ class and a preferred term using the Medical Dictionary for Regulatory Activities (MedDRA).

9.10.2 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. In addition, TEAE with onset during the first 6 months (i.e., 24 weeks or 198 days) of study treatment will be similarly summarized since the treatment for Arm A is 12 IV doses over 24 weeks or until disease progression.

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

For subjects who received cross-over acalabrutinib therapy, all TEAEs collected in the treatment emergent period of cross-over acalabrutinib therapy will be summarized.

9.10.3 AESIs

AESIs are defined in Section 7.2.1.6. These events of interest will be summarized similarly to TEAEs by treatment arms.

9.10.4 Clinical Laboratory Tests

9.10.4.1 Data Summary Methods

For gradable parameters, a summary of worst postbaseline toxicity grade will be provided in the treatment-emergent period and during the first 6 months (6 cycles) of treatment by treatment arm and worst toxicity grade (any Grade and Grade 3/4). The difference in percentages will be displayed. Only subjects whose grades got worsened are counted in the numerator of percentage calculation while the denominator is all subjects in each treatment arm.

9.10.4.2 Analysis of Lymphocytosis

For all subjects with baseline and any post-baseline ALC measurements, ALC at peak summary will be provided by treatment arm.

Lymphocytosis is defined as an ALC > 5000 cells per microliter and an increase above baseline. The number of subjects with at least one occurrence of lymphocytosis will be summarized. For subjects with lymphocytosis, resolution of lymphocytosis is defined as 1) a decrease of ALC value to the baseline level or lower, or 2) an achievement of ALC value that is below 5,000/μL, whichever occurs first. The following analyses will be conducted for subjects with lymphocytosis by treatment arm: ALC at peak and time to peak ALC for subjects who have lymphocytosis will be summarized with descriptive statistics.

Duration of lymphocytosis is defined as the duration of time from the earliest date on which the ALC value met the lymphocytosis criteria at a post-baseline assessment to the earliest date on which a subsequent ALC value met the resolution criteria.

9.10.4.3 Analysis of Serum Immunoglobulins

Serum immunoglobulins (IgA, IgG and IgM) are collected as scheduled in Appendix A, Appendix B, Appendix C, and Appendix D. For each variable, descriptive statistics will be presented at each scheduled post-baseline assessment by treatment arm. Subjects who received IV immunoglobulin on the study will be excluded from the summary for IgG.

9.10.5 ECOG Performance Status

The ECOG performance status will be collected as scheduled in Appendices A-D. The ECOG performance status grade ranges from 0 to 5. Descriptive statistics and change from baseline will be provided for each visit over time.

9.10.6 Vital Signs and Weight

Body temperature, heart rate (beats/min), respiratory rate (breaths/min), systolic blood pressure (mmHg), diastolic blood pressure (mm Hg), and weight will be collected for this study. Those parameters will be collected as scheduled in Appendices A-D. For each parameter, descriptive statistics and change from baseline 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 Title 21 and European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki (October 2008).

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 (e.g., all advertising materials) to the appropriate IRB/IEC for review and approval before study initiation. A signed protocol approval page; a letter confirming IRB/IEC approval of the protocol and informed consent; and a statement that the IRB/IEC is organized and operates according to GCP 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 § 21 Code of Federal Regulations (CFR) Part 50, and other applicable national and local regulations governing informed consent. Each subject must provide a signed and dated informed consent before randomization 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 ICF 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

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

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

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

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 randomized 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 is 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 Investigational New Drug (IND) Safety Reports/SUSAR Reports are submitted promptly to the IRB/IEC.
12. All SAEs are reported to Acerta Pharma Drug Safety/Designee within 24 hours of knowledge 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 Arm A

Appendix A: Schedule of Assessments – Treatment Arm A

		Screening	Treatment Phase										Post-treatment Phase[m]		Treatment and Post-Treatment Phase Response Evaluation	ET/SFU visit[a]	Post-disease Progression Phase
Days			Cycle 1 (28-day cycle)					Cycle 2 (28-day cycle)			Cycles 3-6 (28-day cycles)		Cycle 7 (28-day cycle)	q12 wks starting at Cycle 10 (e.g., Cycles 10, 13, 16)	Assessed q12/q24 wks[b]		q12 wks
			1	2	8	15	22	1	8	15	1	15	1				
Study Windows		-28 days			± 3 days			± 3 days			± 3 days		± 3 days	± 3 days	± 14 days	± 7 days	± 7 days
Study Drug Administration																	
ARM A	Obinutuzumab 100-1000 mg IV		x	x	x	x		x			x						
	Chlorambucil 0.5 mg/kg PO		x			x		x		x	x	x					
Procedures																	
Informed consent		x															
Confirm eligibility & randomize		x															
Medical history		x															
Physical exam		x	x					x			x		x	x	x	x	
ECOG PS		x	x					x			x		x	x		x	
Weight		x	x			x		x		x	x	x	x	x		x	
Cumulative Illness Rating Scale		x															
Disease-related Symptoms		x						x			x		x	x	x		
Vital signs		x	x	x	x	x	x	x	x	x	x	x	x	x		x	
ECG		x															
CCI														CCI			
Concomitant medications		x	x			x		x		x	x	x	x	x		x	
Adverse events[k]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	SAE only
Pregnancy test[d]		x	x													x	
Hepatitis serology[e]		x															

Appendix A: Schedule of Assessments – Treatment Arm A

	Screening	Treatment Phase										Post-treatment Phase[m]		Treatment and Post-Treatment Phase Response Evaluation	ET/SFU visit[a]	Post-disease Progression Phase
Days		Cycle 1 (28-day cycle)					Cycle 2 (28-day cycle)			Cycles 3-6 (28-day cycles)		Cycle 7 (28-day cycle)	q12 wks starting at Cycle 10 (e.g., Cycles 10, 13, 16)	Assessed q12/q24 wks[b]		q12 wks
		1	2	8	15	22	1	8	15	1	15	1				
Study Windows	-28 days			± 3 days			± 3 days			± 3 days		± 3 days	± 3 days	± 14 days	± 7 days	± 7 days
HBV PCR[i]	x						x			QM		x	QM			QM
CCI																
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		x	x		x	
Serum immunoglobulins, β_2-microglobulin, T/B/NK counts	x											x	Every 24 weeks from Cycle 7 (e.g., Cycles 13, 19)[c]	x		
Cytogenetics and genetic molecular prognostic markers	x															
CCI																
CCI													CCI			
CT scans[h]	x[j]													x		
Overall response assessment														x		
Bone marrow biopsy and aspirate	x													To confirm CR[l]		
CCI																
Survival status and new anticancer therapy																x

Abbreviations: ALC = absolute lymphocyte count; ANC = absolute neutrophil count; anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; CR = complete remission (response); CT = computed tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; ET = early termination; CCI HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; Hgb = hemoglobin level; IV = intravenous;IVIG = intravenous immunoglobulins; CCI PCR = polymerase chain reaction; PLT = platelet count;

PO = oral; CCI QM = every month; SFU = safety follow up; wks = weeks.

a. An early termination visit will be done for subjects who permanently discontinue study drug early for any reason (except for death, lost to follow-up, or withdrawal of consent). A safety follow-up visit is conducted 30 (+ 7) days after the last dose of study drug, regardless of whether the subject receives a new anticancer therapy or demonstrates disease progression within this timeframe. If the safety follow-up visit is within ± 7 days of a regularly scheduled visit during the Post-treatment Phase, the visits may be combined into a single visit.

b. Response evaluations will be done every 12 weeks (± 14 days) with the first on-treatment radiologic assessment occurring on Cycle 4 Day 1, the second on-treatment scan on Cycle 7 Day 1, and so on through Cycle 25, and then every 24 weeks (± 14 days) thereafter. Hematology results must be done within 7 days of CT scans. For additional details on the confirmatory bone marrow biopsy for subjects in Arm A, see Minimal Residual Disease/Response Evaluation in Section 7.1.

c. After Cycle 7 Day 1, CCI (through Amendment 5.0), Serum immunoglobulins, β2-microglobulin, T/B/NK counts, and CCI should be collected every 24 weeks starting at Cycle 13.

d. Serum pregnancy tests are required for women with childbearing potential only.

e. Hepatitis serology must include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B core antibody (anti-HBc), and hepatitis C (HCV) antibody. In addition, any subjects testing positive for anti-HBc must have polymerase chain reaction (PCR) testing during screening and on study (see exclusion criterion #14).

f. If these samples are damaged during collection or shipment, they should be redrawn at any subsequent visit.

g. CCI

h. CT scan can be performed up to 7 days before response evaluation.

i. Subjects who are anti-HBc positive should have a quantitative PCR test for HBV DNA performed during screening and every month thereafter. Monthly 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. As intravenous immunoglobulins (IVIG) may cause false positive hepatitis serology, monthly PCR testing is not required in subjects who are currently receiving or received prophylactic IVIG within 3 months before study enrollment and have a documented negative anti-HBc test before the initiation of IVIG therapy. PCR testing should be performed when clinically indicated (e.g., in the setting of rising transaminase levels).

j. 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.

k. After the end of the protocol-defined adverse event reporting period (Section 7.2.2), only serious adverse events considered related to study drug(s) or study procedures are required to be collected.

l. If the subject's physical examination findings, laboratory evaluations, and radiographic evaluations suggest that CR has been achieved, a confirmatory bone marrow aspirate/biopsy and peripheral blood sample must be obtained to confirm the CR and CCI For subjects with bone marrow-confirmed CR, peripheral blood testing to follow CCI until disease progression or death, consent withdrawal, or lost to follow-up.

m. Subjects who stop both drugs early because of an adverse event will then enter an early Post-treatment Phase.

n. CCI

o. Through Amendment 5.0 CCI endpoints were collected and analyzed; with the adaptation of Amendment 6.0, the CCI endpoints will not be collected.

Appendix B: Schedule of Assessments – Treatment Arm B

Appendix B: Schedule of Assessments – Treatment Arm B

		Screening	Treatment Phase[a]									Treatment and Post-treatment Phase[p]		ET/SFU visit[b]	Post-disease Progression Phase
Days			Cycle 1 (28-day cycle)				Cycle 2 (28-day cycle)				Cycles 3-7 (28-day cycles)	q12 wks starting at Cycle 10 (e.g., Cycles 10, 13, 16)	Response Evaluation Assessed q12/q24 wks[c]		q12 wks
			1	8	15	22	1	2	8	15	1				
Study Windows		-28 days	± 3 days				± 3 days		± 3 days		± 3 days	± 3 days	± 14 days	± 7 days	± 7 days
Study Drug Administration															
ARM B	Acalabrutinib 100 mg BID (± 1 hour) PO		Continuous Twice Daily Dosing[d]												
	Obinutuzumab 100-1000 mg IV						x	x	x	x	x				
Procedures															
Informed consent		x													
Confirm eligibility & randomize		x													
Medical history		x													
Physical exam		x	x				x				x	x	x	x	
ECOG PS		x	x				x				x	x		x	
Weight		x	x				x				x	x		x	
Cumulative Illness Rating Scale		x													
Disease-related Symptoms		x					x				x	x	x		
Vital signs		x	x	x	x	x	x	x	x	x	x	x		x	
ECG		x													
CCI												CCI			
Concomitant medications		x	x		x		x			x	x	x		x	
Adverse events[n]			x	x	x	x	x	x	x	x	x	x	x	x	SAE only
Pregnancy test[f]		x	x											x	
Hepatitis serology[g]		x													

Appendix B: Schedule of Assessments – Treatment Arm B

	Screening	Treatment Phase[a]									Treatment and Post-treatment Phase[p]		ET/SFU visit[b]	Post-disease Progression Phase
Days		Cycle 1 (28-day cycle)				Cycle 2 (28-day cycle)				Cycles 3-7 (28-day cycles)	q12 wks starting at Cycle 10 (e.g., Cycles 10, 13, 16)	Response Evaluation Assessed q12/q24 wks[c]		q12 wks
		1	8	15	22	1	2	8	15	1				
Study Windows	-28 days	± 3 days				± 3 days		± 3 days		± 3 days	± 3 days	± 14 days	± 7 days	± 7 days
HBV PCR[l]	x					x				QM	QM			QM
CCI														
Hematology	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	x		x	
Serum immunoglobulins, β_2-microglobulin, T/B/NK counts	x									Cycle 7 only	Every 24 weeks (e.g., Cycles 13, 19)[e]	x		
CCI														
Cytogenetics and genetic molecular prognostic markers	x													
CCI														
CCI											CCI			
CT scans[k]	x[m]											x		
Overall response assessment												x		
Bone marrow biopsy and aspirate	x											To confirm CR[o]		
CCI														
Survival status and new anticancer therapy														x

Abbreviations: ALC = absolute lymphocyte count; ANC = absolute neutrophil count; anti-HBc = hepatitis B core antibody; BID = twice daily; CR = complete remission (response); CT = computed tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; ET = early termination; CCI anti-HBs = 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 PCR = polymerase chain reaction; CCI PLT = platelet count; PO = oral; CCI QM = every month; SFU = safety follow up; wks = weeks.

a. There is no restriction on maximum treatment allowed with acalabrutinib.

b. An early termination visit will be done for subjects who permanently discontinue study drug early for any reason (except for death, lost to follow-up, or withdrawal of consent). A safety follow-up visit is conducted 30 (+ 7) days after the last acalabrutinib dose, regardless of whether the subject receives a new anticancer therapy or demonstrates disease progression within this timeframe. If the safety follow-up visit is within ± 7 days of a regularly scheduled visit during the Post-treatment Phase, the visits may be combined into a single visit.

c. Response evaluations will be done every 12 weeks (± 14 days) with the first on-treatment radiologic assessment occurring on Cycle 4 Day 1, the second on-treatment scan on Cycle 7 Day 1, and so on through Cycle 25, and then every 24 weeks (± 14 days) thereafter. Hematology results must be done within 7 days of CT scans. For additional details on the confirmatory bone marrow biopsy for subjects in Arm B, see CCI Response Evaluation in Section 7.1.

d. Subjects in Arm B will receive 28 days of acalabrutinib monotherapy before beginning obinutuzumab.

e. After Cycle 7 Day 1, CCI (through Amendment 5.0), Serum immunoglobulins, β2-microglobulin, T/B/NK counts, and CCI should be collected every 24 weeks starting at Cycle 13.

f. Serum pregnancy tests are required for women with childbearing potential only.

g. Hepatitis serology must include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B core antibody (anti-HBc), and hepatitis C (HCV) antibody. In addition, any subjects testing positive for anti-HBc must have polymerase chain reaction (PCR) testing during screening and on study (see exclusion criterion #14).

h. If these samples are damaged during collection or shipment, they should be redrawn at any subsequent visit.

i. CCI

j. CCI

k. CT scan can be performed up to 7 days before response evaluation.

l. Subjects who are anti-HBc positive should have a quantitative PCR test for HBV DNA performed during screening and every month thereafter. Monthly 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. As intravenous immunoglobulins (IVIG) may cause false positive hepatitis serology, monthly PCR testing is not required in subjects who are currently receiving or received prophylactic IVIG within 3 months before study enrollment and have a documented negative anti-HBc test before the initiation of IVIG therapy. PCR testing should be performed when clinically indicated (e.g., in the setting of rising transaminase levels).

m. 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.

n. After the end of the protocol-defined adverse event reporting period (Section 7.2.2), only serious adverse events considered related to study drug(s) or study procedures are required to be collected.

o. CCI

CCI [redacted]

p. For subjects who discontinue both study drugs.

q. CCI [redacted]

r. Through Amendment 5.0 CCI endpoints were collected and analyzed; with the adaptation of Amendment 6.0, the PRO endpoints will not be collected.

Appendix C: Schedule of Assessments – Treatment Arm C

Appendix C: Schedule of Assessments – Treatment Arm C

	Screening	Treatment Phase[a]								Treatment and Post-treatment Phase[o]		ET/SFU visit[b]	Post-disease Progression Phase
Days		Cycle 1 (28-day cycle)				Cycle 2 (28-day cycle)			Cycles 3-7 (28-day cycles)	q12 wks starting at Cycle 10 (e.g., Cycles 10, 13, 16)	Response Evaluation Assessed q12/24 wks[c]		q12 wks
		1	8	15	22	1	8	15	1				
Study Windows	-28 days	± 3 days				± 3 days			± 3 days	± 3 days	± 14 days	± 7 days	± 7 days
Study Drug Administration													
ARM C Acalabrutinib 100 mg BID (± 1 hour) PO		Continuous Twice Daily Dosing											
Procedures													
Informed consent	x												
Confirm eligibility & randomize	x												
Medical history	x												
Physical exam	x	x				x			x	x	x	x	
ECOG PS	x	x				x			x	x		x	
Weight	x	x				x			x	x		x	
Cumulative Illness Rating Scale	x												
Disease-related Symptoms	x					x			x	x	x		
Vital signs	x	x	x	x	x	x	x	x	x	x		x	
ECG	x												
CCI										CCI			
Concomitant medications	x	x		x		x		x	x	x		x	
Adverse events[m]		x	x	x	x	x	x	x	x	x	x	x	SAE only
Pregnancy test[e]	x	x										x	
Hepatitis serology[j]	x												
HBV PCR[k]	x					x			QM	QM			QM
CCI													

Appendix C: Schedule of Assessments – Treatment Arm C

	Screening	Treatment Phase[a]								Treatment and Post-treatment Phase[o]		ET/SFU visit[b]	Post-disease Progression Phase
Days		**Cycle 1 (28-day cycle)**				**Cycle 2 (28-day cycle)**			**Cycles 3-7 (28-day cycles)**	**q12 wks starting at Cycle 10 (e.g., Cycles 10, 13, 16)**	**Response Evaluation Assessed q12/24 wks[c]**		**q12 wks**
		1	**8**	**15**	**22**	**1**	**8**	**15**	**1**				
Study Windows	-28 days	± 3 days				± 3 days			± 3 days	± 3 days	± 14 days	± 7 days	± 7 days
Hematology	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		x	
Serum immunoglobulins, β2-microglobulin, T/B/NK counts	x								Cycle 7 only	Every 24 weeks (e.g., Cycles 13, 19)[d]	x		
CCI													
Cytogenetics and genetic molecular prognostic markers	x												
CCI													
CCI										CCI			
CT scans[i]	x[l]										x		
Overall response assessment											x		
Bone marrow biopsy and aspirate	x										To confirm CR[n]		
CCI													
Survival status and new anticancer therapy													x

Abbreviations: ALC = absolute lymphocyte count; ANC = absolute neutrophil count; anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; BID = twice daily; CR = complete remission (response); CT = computed tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; ET = early termination; CCI HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; Hgb = hemoglobin level; IVIG = intravenous immunoglobulins; CCI PCR = polymerase chain reaction; CCI PLT = platelet count; PO = oral; CCI QM = every month; SFU = safety follow up; wks = weeks.

a. There is no restriction on maximum treatment allowed with acalabrutinib.

b. An early termination visit will be done for subjects who permanently discontinue study drug early for any reason (except for death, lost to follow-up, or withdrawal of consent). A safety follow-up visit is conducted 30 (+ 7) days after the last acalabrutinib dose, regardless of whether the subject receives a new anticancer therapy or demonstrates disease progression within this timeframe. If the safety follow-up visit is within ± 7 days of a regularly scheduled visit during the Post-treatment Phase, the visits may be combined into a single visit.

c. Response evaluations will be done every 12 weeks (± 14 days) with the first on-treatment radiologic assessment occurring on Cycle 4 Day 1, the second on-treatment scan on Cycle 7 Day 1, and so on through Cycle 25, and then every 24 weeks (± 14 days) thereafter. Hematology results must be done within 7 days of

CT scans. For additional details on the confirmatory bone marrow biopsy for subjects in Arm C, see CCI Response Evaluation in Section 7.1.

d. After Cycle 7 Day 1, CCI (through Amendment 5.0), Serum immunoglobulins, β2-microglobulin, T/B/NK counts, and CCI should be collected every 24 weeks starting at Cycle 13.

e. Serum pregnancy tests are required for women with childbearing potential only.

f. If these samples are damaged during collection or shipment, they should be redrawn at any subsequent visit.

g. CCI

h. CCI

i. CT scan can be performed up to 7 days before response evaluation.

j. Hepatitis serology must include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B core antibody (anti-HBc), and hepatitis C (HCV) antibody. In addition, any subjects testing positive for anti-HBc must have polymerase chain reaction (PCR) testing during screening and on study (see exclusion criterion #14).

k. Subjects who are anti-HBc positive should have a quantitative PCR test for HBV DNA performed during screening and every month thereafter. Monthly 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. As intravenous immunoglobulins (IVIG) may cause false positive hepatitis serology, monthly PCR testing is not required in subjects who are currently receiving or received prophylactic IVIG within 3 months before study enrollment and have a documented negative anti-HBc test before the initiation of IVIG therapy. PCR testing should be performed when clinically indicated (e.g., in the setting of rising transaminase levels).

l. 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.

m. After the end of the protocol-defined adverse event reporting period (Section 7.2.2), only serious adverse events considered related to study drug(s) or study procedures are required to be collected.

n. If the subject's physical examination findings, laboratory evaluations, and radiographic evaluations suggest that CR has been achieved, a confirmatory bone marrow aspirate/biopsy and peripheral blood sample must be obtained to confirm the CR and to evaluate minimal residual disease by flow cytometric and DNA based methods. For subjects with bone marrow-confirmed CR, peripheral blood testing to follow CCI until disease progression or death, consent withdrawal, or lost to follow-up.

o. For subjects who discontinue study drug.

p. CCI

q. CCI

Appendix D: Schedule of Assessments – Crossover

Appendix D: Schedule of Assessments – Crossover

	Screening	Treatment Phase[a]								Treatment and Post-treatment Phase[i]		ET/SFU visit[b]	Post-disease Progression Phase
		Cycle 1 (28-day cycle)				Cycle 2 (28-day cycle)			Cycles 3-7 (28-day cycles)	q12 wks starting at Cycle 10 (e.g., Cycles 10, 13, 16)	Response Evaluation Assessed q12/q24 wks[c]		q12 wks
Days		1	8	15	22	1	8	15	1				
Study Windows	-42 days	± 3 days				± 3 days			± 3 days	± 3 days	± 14 days	± 7 days	± 7 days
Study Drug Administration													
CROSSOVER Acalabrutinib 100 mg BID PO		Continuous Twice Daily Dosing											
Procedures													
Physical exam	x	x				x			x	x	x	x	
ECOG PS	x	x				x			x	x		x	
Weight	x	x				x			x	x		x	
Disease-related Symptoms	x										x		
Vital signs	x	x	x	x	x	x	x	x	x	x		x	
ECG	x												
Concomitant medications	x	x		x		x		x	x	x		x	
Adverse events[g]		x	x	x	x	x	x	x	x	x	x	x	SAE only
Pregnancy test[d]	x	x										x	
HBV PCR[e]	x					x			QM	QM		QM	
CCI													
Hematology	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		x	
Serum immunoglobulins, β2-microglobulin, T/B/NK counts	x												
Cytogenetics and genetic molecular prognostic markers	x												
CCI													

Appendix D: Schedule of Assessments – Crossover

	Screening	Treatment Phase[a]								Treatment and Post-treatment Phase[i]		ET/SFU visit[b]	Post-disease Progression Phase
		Cycle 1 (28-day cycle)				Cycle 2 (28-day cycle)			Cycles 3-7 (28-day cycles)	q12 wks starting at Cycle 10 (e.g., Cycles 10, 13, 16)	Response Evaluation Assessed q12/q24 wks[c]		q12 wks
Days		1	8	15	22	1	8	15	1				
Study Windows	-42 days	± 3 days				± 3 days			± 3 days	± 3 days	± 14 days	± 7 days	± 7 days
CT scans[f]	x[f]										x[f]		
Overall response assessment											x		
Bone marrow biopsy and aspirate											To confirm CR[h]		
CCI													
Survival status and new anticancer therapy													x

Abbreviations: ALC = absolute lymphocyte count; ANC = absolute neutrophil count; anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; BID = twice daily; CR = complete remission (response); CT = computed tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; ET = early termination; CCI HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; Hgb = hemoglobin level; IVIG = intravenous immunoglobulins; CCI PCR = polymerase chain reaction; CCI PLT = platelet count; PO = oral; CCI QM = every month; SFU = safety follow up; wks = weeks.

a. There is no restriction on maximum treatment allowed with acalabrutinib.

b. An early termination visit will be done for subjects who permanently discontinue study drug early for any reason (except for death, lost to follow-up, or withdrawal of consent). A safety follow-up visit is conducted 30 (+ 7) days after the last acalabrutinib dose, regardless of whether the subject receives a new anticancer therapy or demonstrates disease progression within this timeframe. If the safety follow-up visit is within ± 7 days of a regularly scheduled visit during the Post-treatment Phase, the visits may be combined into a single visit.

c. Response evaluations will be done every 12 weeks (± 14 days) with the first on-treatment radiologic assessment occurring on Cycle 4 Day 1, the second on-treatment scan on Cycle 7 Day 1, and so on through Cycle 25, and then every 24 weeks (± 14 days) thereafter. Hematology results must be done within 7 days of CT scans. For additional details on the confirmatory bone marrow biopsy for subjects in Arm D, see CCI Response Evaluation in Section 7.1.

d. Serum pregnancy tests are required for women with childbearing potential only.

e. Subjects who are anti-HBc positive should have a quantitative PCR test for HBV DNA performed during screening and every month thereafter. Monthly 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. As intravenous immunoglobulins (IVIG) may cause false positive hepatitis serology, monthly PCR testing is not required in subjects who are currently receiving or received prophylactic IVIG within 3 months before study enrollment and have a documented negative anti-HBc test before the initiation of IVIG therapy. PCR testing should be performed when clinically indicated (e.g., in the setting of rising transaminase levels).

f. CT scans that showed disease progression from Arm A can be used for the crossover screening CT scan, if within 60 days of crossover dosing Cycle 1 Day 1. CT scan can be performed up to 7 days before response evaluation.

g. After the end of the protocol-defined adverse event reporting period (Section 7.2.2), only serious adverse events considered related to study drug(s) or study procedures are required to be collected.

h. If the subject's physical examination findings, laboratory evaluations, and radiographic evaluations suggest that CR has been achieved, a confirmatory bone marrow aspirate/biopsy and peripheral blood sample must be obtained to confirm the CR and to evaluate minimal residual disease by flow cytometric and DNA-based assay. For subjects with bone marrow-confirmed CR, peripheral blood testing to follow CCI until disease progression or death, consent withdrawal, or lost to follow-up.

i. The Post-treatment Phase begins when the subject stops acalabrutinib.

j. CCI

Appendix E: 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, e.g., 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 self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

* 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. *J Clin Oncol*. 1982;5:649-655.

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

Appendix F: 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.

c. After discontinuation of the strong or moderate CYP3A inhibitor, wait 3 days before resuming ventoclax or acalabrutinib.

Strong Inducers of CYP3A	Moderate Inducers of CYP3A
Carbamazepine	bosentan
Enzalutamide	efavirenz
Mitotane	etravirine
Phenytoin	modafinil
Rifampin	
St. John's wort[a]	

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

P-gp Inhibitors	BCRP Inhibitors	Narrow Therapeutic Index P-gp Substrates
Amiodarone	curcumin	digoxin
Carvedilol	cyclosporine A	everolimus
Clarithromycin	eltrombopag	sirolimus
Dronedarone		
Itraconazole		
Lapatinib		
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 G: Response Assessment Criteria (modified from Hallek 2008)

Response	Lymphocytes	Bone Marrow	Physical Exam[a] (Nodes, Liver, Spleen)	Peripheral Blood
CR*	Lymphocytes < 4 x 10^9/L	Normocellular < 30% lymphocytes No B-lymphoid nodules	Normal (e.g., no lymph nodes > 1.5 cm)	ANC > 1.5 x 10^9/L[b] Platelets > 100 x 10^9/L[b] Hemoglobin > 11.0 g/dL (untransfused)[b]
CRi	Lymphocytes < 4 x 10^9/L	Hypocellular < 30% lymphocytes No B-lymphoid nodules	Normal (e.g., no lymph nodes > 1.5 cm)	Persistent anemia, thrombocytopenia, or neutropenia related to drug toxicity
nPR	CR with the presence of B-lymphoid nodules in the bone marrow which reflect residual disease			
PR*	Lymphocytes < 5 x 10^9/L Or ≥ 50% decrease from baseline	Not assessed	≥ 50% reduction in lymphadenopathy[c] and/or in spleen or liver enlargement	ANC > 1.5 x 10^9/L Or Platelets > 100 x 10^9/L or ≥ 50% improvement over baseline[b] Or Hemoglobin > 11.0 g/dL or ≥ 50% improvement over baseline (untransfused)[b]
PRL*	Lymphocytes ≥ 5 x 10^9/L AND <50% decrease from baseline	Not assessed	≥ 50% reduction in lymphadenopathy[c] and/or in spleen or liver enlargement	ANC > 1.5 x 10^9/L Or Platelets > 100 x 10^9/L or ≥ 50% improvement over baseline[b] Or Hemoglobin > 11.0 g/dL or ≥ 50% improvement over baseline (untransfused)[b]
SD	Absence of PD and failure to achieve at least a PR			
PD*	Lymphocytes ≥ 50% increase over baseline, with ≥ 5000 B lymphocytes/µL	Not assessed (except to confirm PD as assessed by progressive cytopenias)	Appearance of any new lesion or de novo appearance of hepatomegaly or splenomegaly Or Increase ≥ 50% in lymphadenopathy Or Increase ≥ 50% in hepatomegaly Or Increase ≥ 50% in splenomegaly	Platelets decrease of ≥ 50% from baseline secondary to CLL or < 100,000/uL and worsening bone marrow due to CLL Or Hemoglobin decrease of > 2 g/dL from baseline secondary to CLL or decrease to < 100 g/L and worsening bone marrow due to CLL

Abbreviations: ANC = absolute neutrophil count; CLL= chronic lymphocytic leukemia; CR = complete remission (response); CRi = CR with incomplete bone marrow recovery; nPR = nodular partial remission; PD = progressive disease; PR = partial remission (response); PRL = partial remission (response) with lymphocytosis; SD = stable disease.

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

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

b. Without need for exogenous growth factors

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

Appendix H: 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.

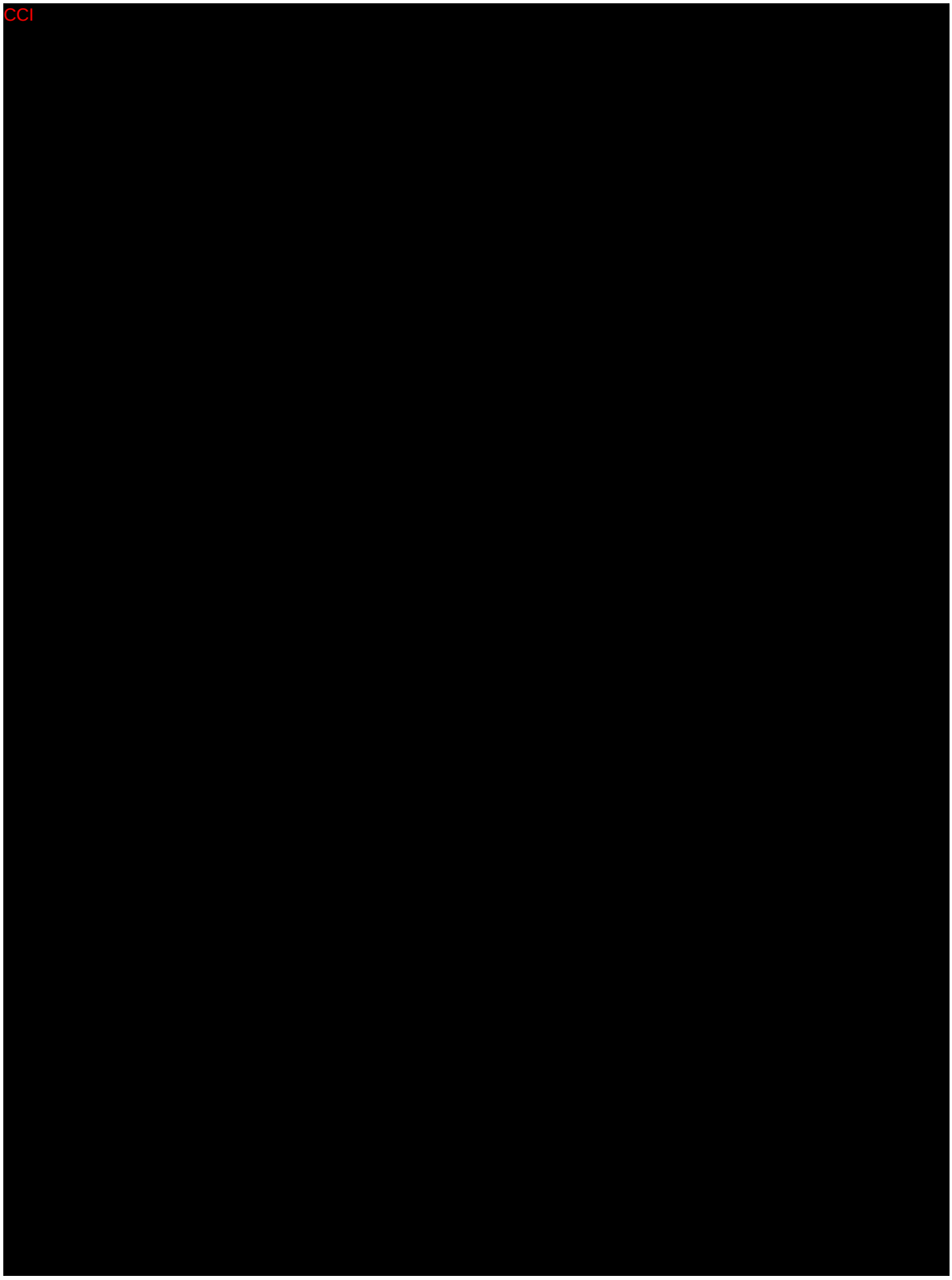
Yes = There is a reasonable possibility that the event may have been caused by study drug.

The adverse event:

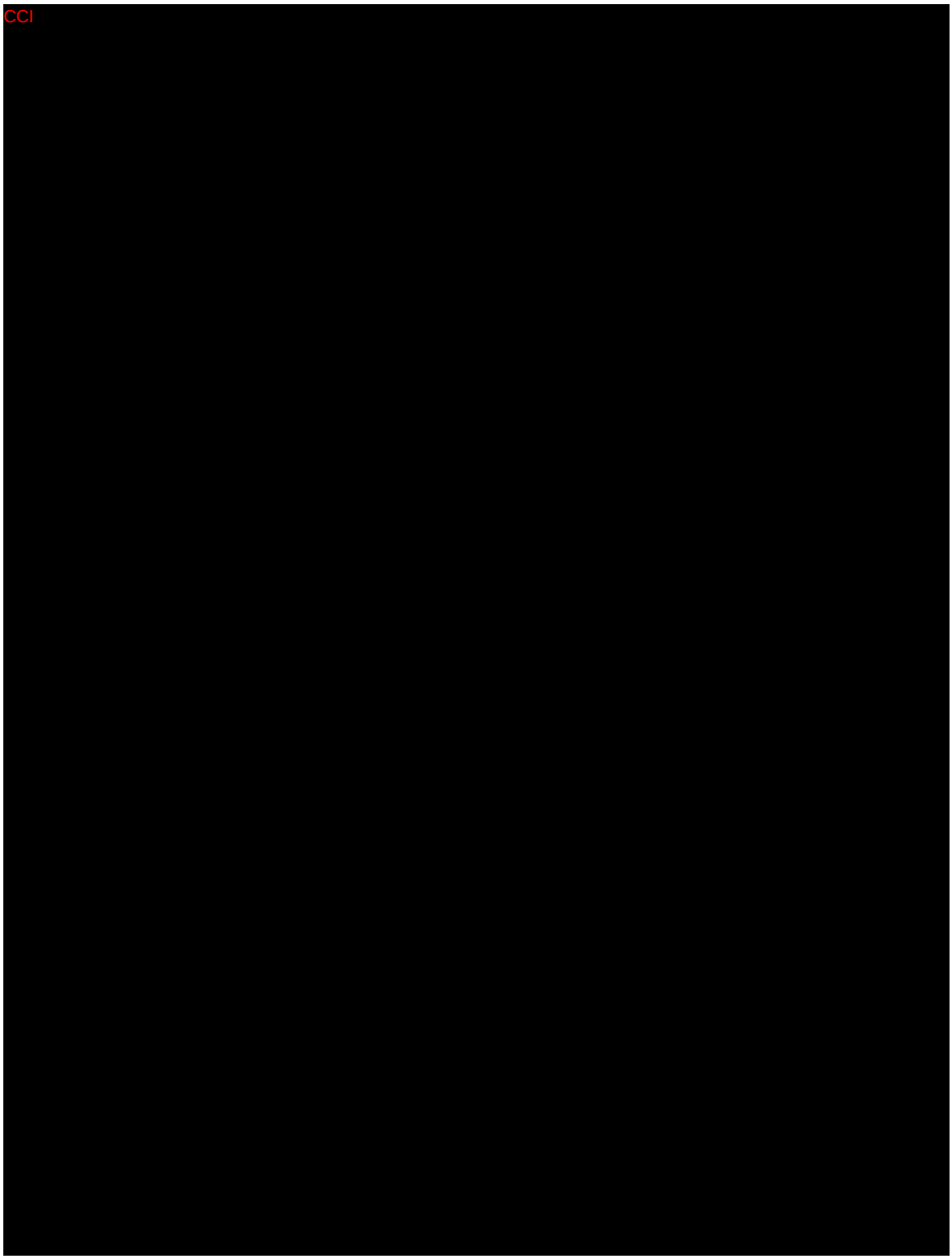
- follows a temporal sequence from administration of study drug.
- is a known response to the study drug based on clinical or preclinical data.
- could not be explained by the known characteristics of the subject’s clinical state, environmental or toxic factors, or other therapy administered to the subject.
- disappears or decreases upon cessation or reduction of dose of study drug.
- reappears or worsens when study drug is re-administered.

Appendix I: CCI
(through Amendment 5.0)

CCI

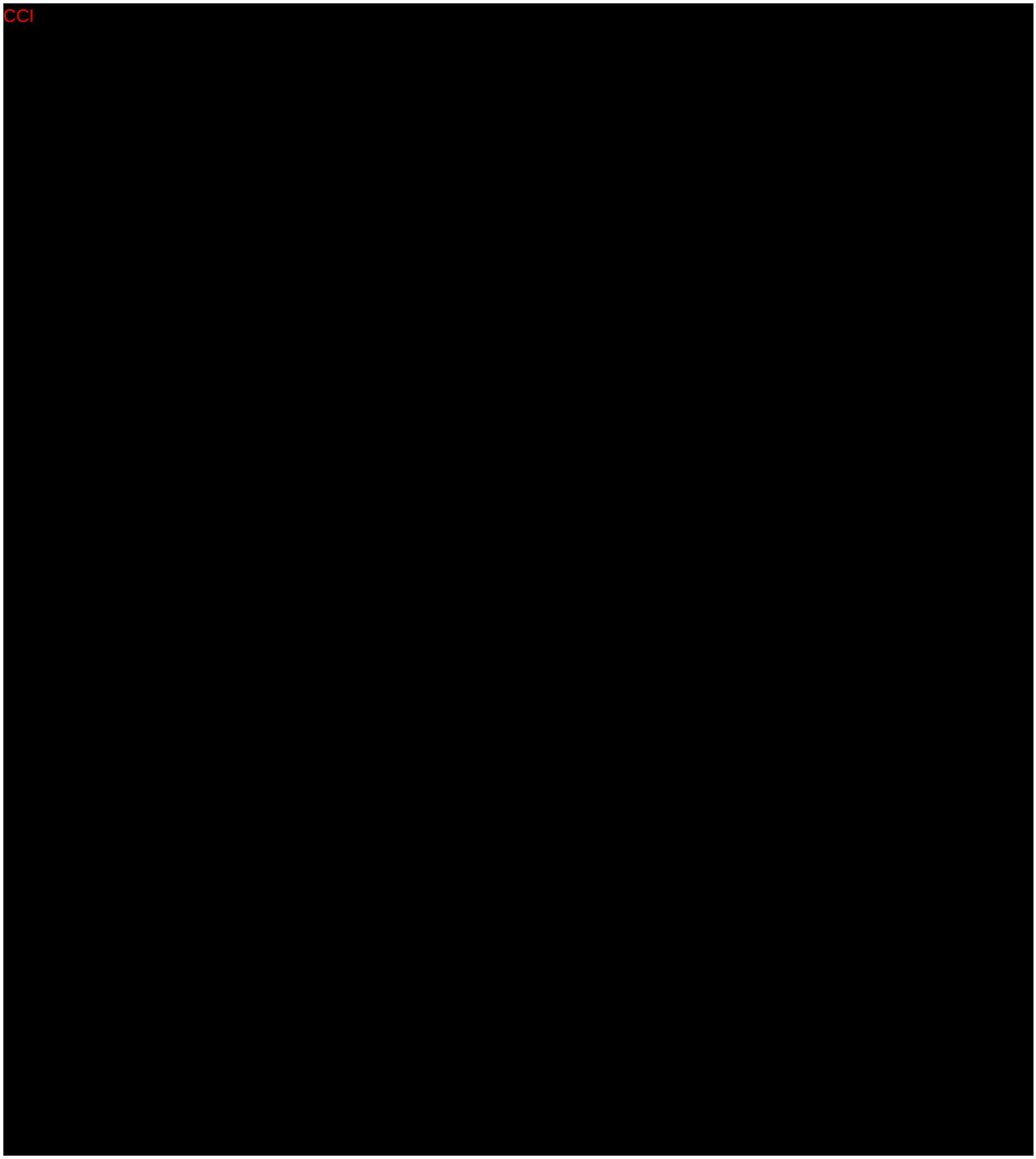


CCI



Appendix J: CCI
(through Amendment 5.0)

CCI

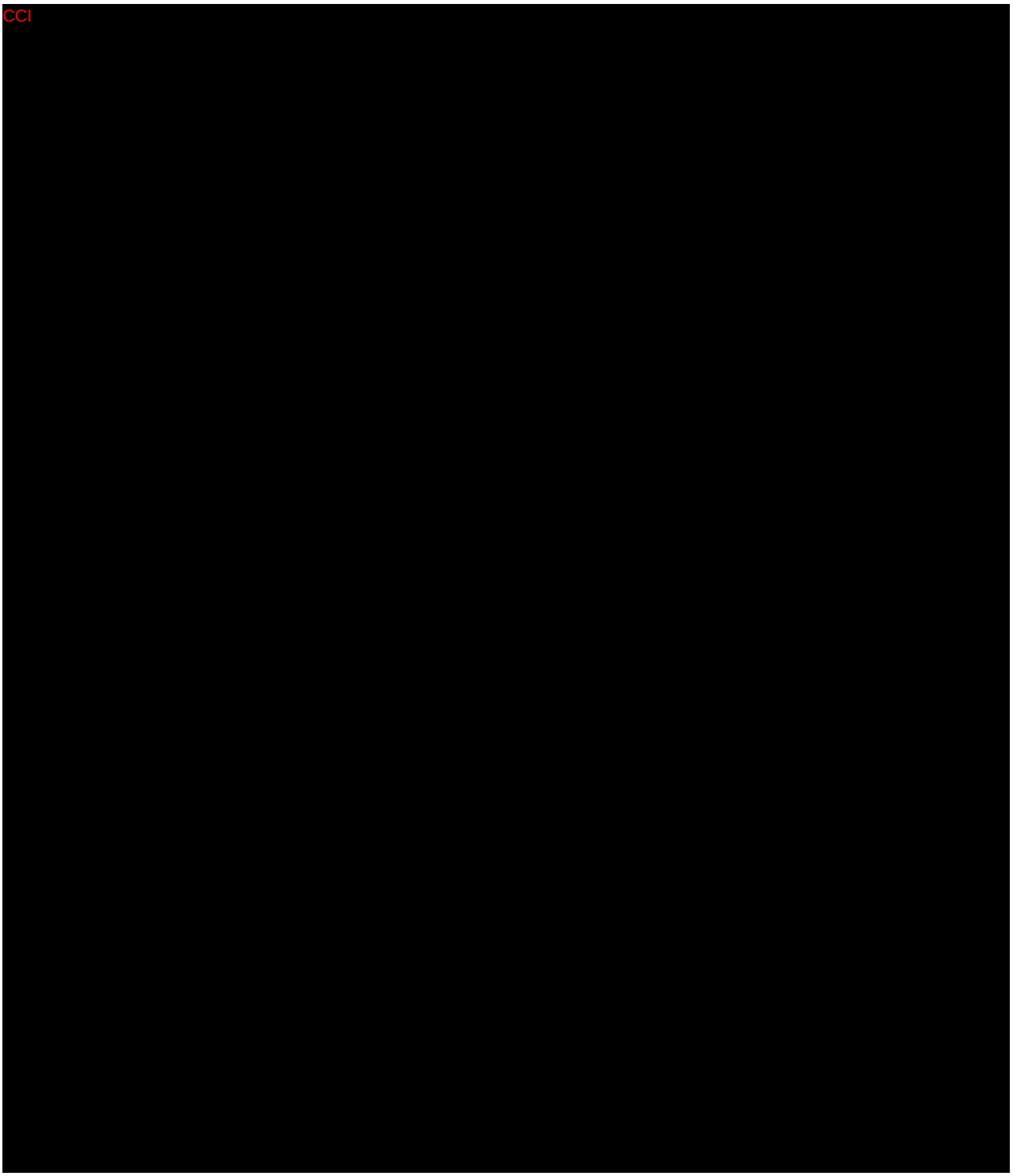


CCI

[redacted]

Appendix K: CCI
(through Amendment 5.0)

CCI



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

Web-based CIRS-G calculator link:
http://eforms.moffitt.org/cirsgScore.aspx

SAOP - CIRS-G Score Calculator -redirect - H. Lee Moffitt Cancer Center & Research Institute - H. Lee Moffitt Canc... Page 1 of 1

CIRS-G Score Calculator

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

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

Patient: **Age:**

Rater: **Date:** 12/19/2011

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

Rating Malignancies

Unlisted Diseases

Submit

http://www.moffitt.org/Site.aspx?spid=4ACED188A74146C996083374C88849CC&type=cirsgScore 12/29/2011

Appendix M: Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

INTRODUCTION

This Appendix describes the process to be followed in order 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, together with the sponsor, in 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 other 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 *PHL* case as an SAE of Potential Hy's law; seriousness criteria "Important medical event" and causality assessment "yes/related" or in accordance with the clinical study protocol as appropriate.
- Request a repeat of the test (new blood draw) without delay
- Complete the appropriate unscheduled laboratory 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 was initially detected, the study Medical Monitor and 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"), 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 agreed plan. After the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are *still* met. Update the previously submitted PHL SAE report following the clinical study protocol process, according to the outcome of the review.

ACTIONS REQUIRED FOR REPEAT EPISODES OF POTENTIAL HY'S LAW

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

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

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

- If the answer is **No**:

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

- If the answer is **Yes**:

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

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

LABORATORY TESTS

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

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

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

REFERENCES

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

Appendix N: Management of Study Procedures During Pandemic

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

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

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

Study Subject Participation

Conduct of Telephone Visits

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

Acalabrutinib Dose Modification Recommendation for COVID-19

The sponsor recognizes that coronavirus 2019-nCoV (COVID-19) presents an increased risk for all patients. Due to the potential impact of COVID-19 on multiple organ systems, the sponsor

recommends the following dose modification and management plan for patients with confirmed or suspected COVID-19 while receiving treatment with acalabrutinib.

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

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

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

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

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

Please contact the study medical monitor for further discussion.

Comparator Drugs or Drugs used in Combination with Acalabrutinib

- Please refer to guidance from the manufacturer.

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

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

- The potential combination with chloroquine or 8-8-OH-chloroquine (8-OH-CHQ) and azithromycin are not predicted to have a pharmacokinetic DDI with acalabrutinib. However, both agents are known to cause cardiovascular risk of QT prolongation.

Therefore, the risk/benefit of initiating 8-OH-CHQ + azithromycin should be discussed with the medical monitor.

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

COVID-19 Specific Data Entry Instructions for Investigational Sites

Adverse Event Recording

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

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

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

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

Study Treatment Recording

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

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

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

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

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

Capturing Telephone Contacts with Subjects

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

1. If the visit is specified as a phone visit as per protocol, no additional action is required.
2. If the visit is listed as on-site but the subject will be contacted by phone, data should be completed as per a normal visit (i.e., using the relevant eCRF pages to capture a phone Visit Date), and any possible assessment that can be obtained remotely should be captured, such as AEs, study drug administration and/or concomitant medications, and any additional safety information. All assessments that cannot be performed should be

marked as not done or eCRF inactivated/marked Blank. A protocol deviation should be recorded in the clinic notes prefixed COVID19 detailing the use of a phone visit in place of an onsite visit.

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

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

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

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

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

- The pharmacy completes its accountability with each shipment made directly to a subject.